Volume 30 No. 6 June, 1960

JOURNAL OF GENERAL CHEMISTRY of the USSR

ЖУРНАЛ ОБЩЕЙ ХИМИИ
(ZHURNAL OBSHCHEI KHIMII)

TRANSLATED FROM RUSSIAN

CONSULTANTS BUREAU

Volume 30, No. 6

June, 1960

JOURNAL OF GENERAL CHEMISTRY OF THE USSR

(ZHURNAL OBSHCHEI KHIMII)

A publication of the Academy of Sciences of the USSR

IN ENGLISH TRANSLATION

Year and issue of first translation:
Vol. 19 No. 1 January 1949

	U. S. and Canada	*Foreign*
Annual Subscription	*$120.00*	*$125.00*
Annual subscription for libraries of nonprofit academic institutions	*50.00*	*55.00*
Single issue	*15.00*	*15.00*

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Printed in the United States of America

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PREPARATION OF NONHYDROXYLATED SOLVENTS WITH A VERY LOW WATER CONTENT

Ya. I. Chulkov

Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1753-1755,
June, 1960
Original article submitted June 7, 1959

The dehydration of low-boiling solvents like ether, acetone, benzene, chloroform, carbon tetrachloride, and other commercial solvents not containing hydroxyl groups is usually done by either shaking or heating them over various drying agents (metallic sodium, phosphorus pentoxide, calcium oxide, calcium and sodium sulfates, sulfuric acid, etc.). However, this process consumes a lot of time, and an adequately complete dehydration of the solvent is not always achieved; using the above mentioned drying agents, it is possible to reduce the water content down to a matter of 0.5 to 0.05%. If it is necessary to have exceedingly dry materials with a water content of 0.005% or less, then the known drying agents cannot be used [1]. Very little information exists in the literature regarding the preparation of solvents with a very low water content, although the problem of the effect of trace amounts of water on chemical reactions is well known [2].

As had been established by us, the most complete dehydration of nonhydroxylated solvents may be achieved by decomposing lead tetraacetate with the water contained in the solvent [3]. In this case the water of the solvent is firmly bound in accordance with the equation

$$2H_2O + (CH_3COO)_4Pb \longrightarrow PbO_2 + 4CH_3COOH.$$

The heavy precipitate of lead dioxide that separates here can be recycled after fractional distillation of the solvent.

Lead tetraacetate is synthesized chemically by treating red lead oxide with glacial acetic acid [4-6] in a vessel, well protected from atmospheric moisture, which is equipped with a stirrer, thermometer, reflux condenser, and a source of heat. The reaction is exothermic. The rate of the reaction is regulated so that the temperature of the vessel contents does not exceed 65°. The clear solution is cooled without admitting air; a substantial amount of colorless lead tetraacetate separates here. In order to separate this salt, the liquid found underneath it is decanted as completely as possible, and then the crystals are separated from the mother liquor by suction-filtration.

A somewhat less pure fraction of the salt can be obtained from the mother liquor by treating the latter with a stream of dry chlorine.

Recently a simpler method has been devised for the synthesis of lead tetraacetate, consisting in the electrochemical oxidation of lead diacetate at the anode [10]. Here the electrolyte is a solution of 2.1 N $Pb(CH_3COO)_2$ and 0.6 N CH_3COOK in anhydrous acetic acid. The electrolysis is conducted at an anodic current density of 3 amp/sq dm and a temperature of 80-85° (artificial cooling is necessary). The voltage on the electrolyzer is about 100 v.

As is known, the efficiency of a drying agent depends on the vapor pressure of the hydrated compound, on the physical state of the drying agent, and also on the way that it is used. Dehydration in the liquid phase is more effective than drying as the vapors. To dehydrate a solvent using lead tetraacetate, the latter is added in

TABLE 1

Amount of Water in Solvents that Had Been Dehydrated Using the Common Drying Agents (taken from [3])

Solvent	Amt. of water in g/100 ml of solvent
Benzene	$6.90 \cdot 10^{-3}$
	$7.20 \cdot 10^{-3}$
Pyridine	$3.46 \cdot 10^{-2}$
	$3.40 \cdot 10^{-2}$
Diethyl ether	$2.54 \cdot 10^{-2}$
	$2.50 \cdot 10^{-2}$
Dimethyl ketone	$6.60 \cdot 10^{-2}$
	$6.56 \cdot 10^{-2}$

TABLE 2

Amount of Water in Solvents that Had Been Dehydrated With Lead Tetraacetate

Solvent	Amt. of water in 100 ml of solvent (in g)		
	added	found	difference
Pyridine	0.3776	0.3762	$9.0 \cdot 10^{-4}$
Diethyl ether	0.4368	0.4354	$1.4 \cdot 10^{-3}$
Dimethyl ketone	0.4717	0.4691	$1.6 \cdot 10^{-3}$

slight excess of theory to the vessel containing the solvent. The reaction mixture is stirred vigorously with heating at the boiling point of the solvent, but not above 85°, for 30 min.

A convenient way of distilling the solvent in a well dried apparatus, not permitting contact with moist air, is fractional distillation. The possibility of using this method as regards organic solvents is determined by several factors. With other conditions constant, the greater the difference between the boiling point of acetic acid and the solvent and the more efficient the distillation column, the purer will be the distilled solvent.

The amount of water remaining in a nonhydroxylated solvent is the main criterion in estimating the efficiency of a drying agent. The amount of water in some nonhydroxylated solvents after their dehydration using the common drying agents is given in Table 1.

At a very low water content in the organic solvent, the quantitative determination of the water becomes difficult, for which reason we added known (slight) amounts of water to the solvent samples that had been dehydrated using lead tetraacetate, and then redetermined the water. The results are given in Table 2.

The obtained results indicate that use of lead tetraacetate is a quite reliable way of effecting the chemical dehydration of nonhydroxylated solvents. The dehydration of different nonhydroxylated solvents goes to variable degree, but always very completely, since the residual amount of water (with practically complete absence of acidity) does not exceed 10^{-3} g in 100 ml of solvent; the practical removal of water from nonhydroxylated solvents reaches 1 : 10,000.

SUMMARY

1. The use of lead tetraacetate as a drying agent for nonhydroxylated organic solvents (pyridine, diethyl ether, dimethyl ketone) was investigated.

2. It was shown that the use of lead tetraacetate makes it possible to achieve a high degree of dehydration of the indicated solvents. Depending on the nature of the solvent, the amount of residual water varies somewhat, but it does not exceed 10^{-3} g per 100 ml.

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PHYSICOCHEMICAL INVESTIGATION OF DIOXANE-CONTAINING SYSTEMS

XII. NEW METHOD FOR THE PREPARATION OF SULFUR TRIOXIDE DIOXANATE

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1755-1757, June, 1960
Original article submitted June 11, 1959

The sulfonation of organic compounds using a complex of sulfur trioxide assumes constantly increasing theoretical and practical significance, as is evidenced by a number of papers [1-3]. Dioxane sulfotrioxide, proposed as an agent for the sulfonation of a number of organic compounds [4], possesses considerable interest in this respect. For this purpose two dioxanates: $O(CH_2CH_2)_2OSO_3$ and $O_3S(CH_2CH_2)_2OSO_3$, were isolated from carbon tetrachloride and ethylene chloride solutions. Suter [4] mentions that great difficulties are encountered in obtaining the dioxanates of sulfur trioxide by the direct reaction of these addenda due to "considerable charring." To eliminate this phenomenon, Suter first dissolved the dioxane in an inert solvent (carbon tetrachloride or ethylene chloride), then bubbled in the sulfur trioxide, and isolated the dioxanates as white flocculent precipitates.

Our purpose was to study the possibility of obtaining the dioxane complexes of sulfur trioxide in the absence of a solvent, not in the liquid phase, but in the gas phase.

EXPERIMENTAL

The starting materials were prepared the same as before [5]. The apparatus used for the synthesis was an inverted U-shaped tube with a diameter of about 1.5 cm and a height of about 10 cm. Two small beakers with ground-glass connections were installed in the openings of the tube. Dry crystals of solid sulfur trioxide were placed in one of the beakers, while liquid dioxane was placed in the other. Within 5-7 min a snow-white solid, representing the complex of dioxane with sulfur trioxide, began to condense copiously on the internal walls of the tube, directly over the dioxane. Here neither charring nor even a yellowing of the product was observed. The complex that formed during reaction tended to condense in the bend of the tube on the dioxane side as a ring with a steadily smaller hole, and already within 30 min this hole was almost completely plugged with a loose white deposit. After 35 min the beaker with dioxane was removed, and the main mass of the deposit was transferred as rapidly as possible to a dry, tared container, and a capillary was also filled with the material for determining the melting point. The beaker with dioxane was then replaced tightly in the tube.

The deposit in the beaker weighed 0.0250 g. The complex is decomposed by water to yield sulfuric acid. The obtained aqueous solution was completely colorless. The amount of sulfuric acid in the aqueous solution was titrated with 0.1304 N NaOH solution in the presence of phenolphthalein. The amount of alkali consumed for the indicated weight of the complex was 2.7 ml. In a similar manner, using the same or different time intervals, additional samples of the complex were collected, and each sample was analyzed for the amount of sulfur trioxide, and also for the amount of dioxane (by difference). A total of six analyses was made in this experiment, which lasted approximately 4 days.

Composition of Complexes of Type $(SO_3)_x \cdot (C_4H_8O_2)_y$

Sample No.	Length of experiment	Wt. of material (in g) and its appearance	Found in complex (mole · 10^3)			Melting point
			sulfur trioxide(x)	dioxane (y)	$\frac{x}{y}$	
		Experiment 1				
1	35 min	0.0250 snow-white, dry	0.175	0.124	1.41	
2	1.5 hr	0.0198	0.117	0.118	0.99	Slight browning at 79°
3	3 hr	0.0187 snow-white, dry, crumbly	0.110	0.112	0.99	
4	4.5hr	0.0102	0.065	0.057	1.17	Slight browning at 45°
5	2.5 days	0.1398 white, tendency to mat	0.459	1.17	2.5	
6	3.5 days	0.0254 white, dry	0.104	0.193	2.39	
		Experiment 2				
7	50 min	0.0169	0.124	0.700	1.77	
8	1 hr 50 min	0.0186	0.131	0.092	1.40	
9	2 hr 20 min	0.0021	0.019	0.0067	2.8	
10	3 hr 40 min	0.0137	0.125	0.52	1.96	
11	4 hr	0.0238	0.137	0.146	0.93	57°
12	5 hr	0.0241	0.141	0.143	0.99	60° (fusion)
13	6 hr	0.0108	0.068	0.060	1.11	Slight browning with fusion at 76°
14	7 hr	0.1931	1.18	1.09	1.09	
15	8 hr	0.1083	0.438	0.83	0.53	

The molar ratios of the addenda in the complex $(SO_3)_x \cdot (C_4H_8O_2)_y$ were also calculated from the analysis results (see table).

From the analysis data for Sample 1 it can be seen that at first the complex contains excess SO_3, i.e., $x > y$ by nearly 1.5 times.

The analysis data obtained for Samples 2-4 indicate that with further reaction the dioxane vapors react with the sulfur trioxide vapors to give a molecular compound of constant composition, with $x = y = 1$. Consequently, the empirical formula of this compound is $C_4H_8O_2 \cdot SO_3$.

Repeated determination of the melting point in the usual manner revealed that the small white crystals begin to change to a glass in the capillary at about 57-60°. No indications of charring were observed here. On further heating, the solid changes completely to a liquid in the range 74-79°. Here the liquid turns brown. Consequently, the compound $SO_3 \cdot C_4H_8O_2$ shows no tendency to char at room temperature. Only at temperatures close to the melting point does the compound become unstable, since here the sulfur trioxide begins to oxidize the dioxane. From the data in the table it can also be seen that with further progress of synthesis in the gas phase the complex again begins to contain an excess of sulfur trioxide, since $x > y$ (Samples 5 and 6).

In contrast to Expt. 1, in Expt. 2 the small beaker was filled with liquid sulfur trioxide. The liquid SO_3 crystallized (polymerized) in the beaker. A part of the SO_3 crystals collected on the walls of the tube at the bend over the beaker with SO_3 (up to half of its height). Immediately after the small beaker with dioxane was installed, a snow-white deposit of the sulfur trioxide dioxanate began to collect on the walls of the tube above the beaker. Because of the smaller surface of the fused solid SO_3 the rate of formation of the complex in Expt. 2 was slower than in Expt. 1. To hasten the evaporation of both the SO_3 and the dioxane, both beakers were kept at 30-35°. Within 45-50 min the white deposit almost filled the entire cross-section area of the tube at a height of 2 cm above the beaker containing the sulfur trioxide. Then, the same as in Expt. 1, individual samples of the obtained complex were removed at random intervals, and analyzed as already indicated. The data for Expt. 2 (Sample Nos. 7-15) are also given in the table.

From the obtained experimental data we arrive at the conclusion that the ratio of the addenda in the formed complex varies ($\frac{x}{y}$ = 2, 1, 0.5); consequently, since it polymerizes readily in the free state, sulfur trioxide reacts with dioxane (the same as when it reacts with water) to give not one, but a series of compounds.

SUMMARY

1. A method was proposed for obtaining the complex of dioxane with sulfur trioxide by the direct reaction of dioxane vapors with sulfur trioxide vapors, excluding charring of the final product.

2. Based on the analysis data, the ratio of the addenda in the complex of sulfur trioxide to dioxane is expressed mainly by the numbers 2 and 1.

3. The rate with which the indicated complex is formed can be easily changed by varying the temperature, which leads to changing the rate with which the dioxane and sulfur trioxide vaporize.

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SYNTHESIS OF HYDROCARBONS

LXXIV. ALKYLCYCLOHEXANES WITH TWO QUATERNARY CARBON ATOMS IN THE SIDE CHAIN

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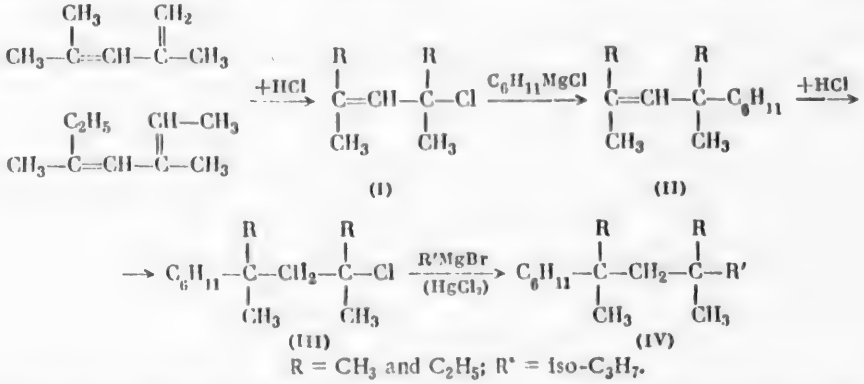
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1758-1761, June, 1960
Original article submitted June 24, 1959

From the standpoint of selecting the optimum structures of hydrocarbons capable of functioning as possible components of motor fuel considerable interest is possessed by the alkylcyclohexanes with a highly branched side chain, characterized by having a high density and a low freezing point [1]. It had been shown in our previous papers [2-5] that alkanes with two quaternary carbon atoms, separated by a methylene group (di-tert-alkylmethanes), have constants ($n^{20}D$, d^{20}_4) that are considerably higher than those possessed by isomeric hydrocarbons also containing two quaternary carbon atoms, but at a greater distance from each other [6].

In the present paper we synthesized some di-tert-alkylmethanes in which one of the tert-alkyl radicals contained a cyclohexyl group. Hydrocarbons of such structure, being alkylcyclohexanes with two quaternary carbon atoms in the side chain, were synthesized by the scheme that we had proposed earlier [2-5] for synthesizing di-tert-alkylmethanes; as starting materials we used the tertiary allyl chlorides (I):(the hydrochlorides of conjugated alkadienes of 2,4-dimethyl-1,3-pentadiene and 3,5-dimethyl-2,4-heptadiene).

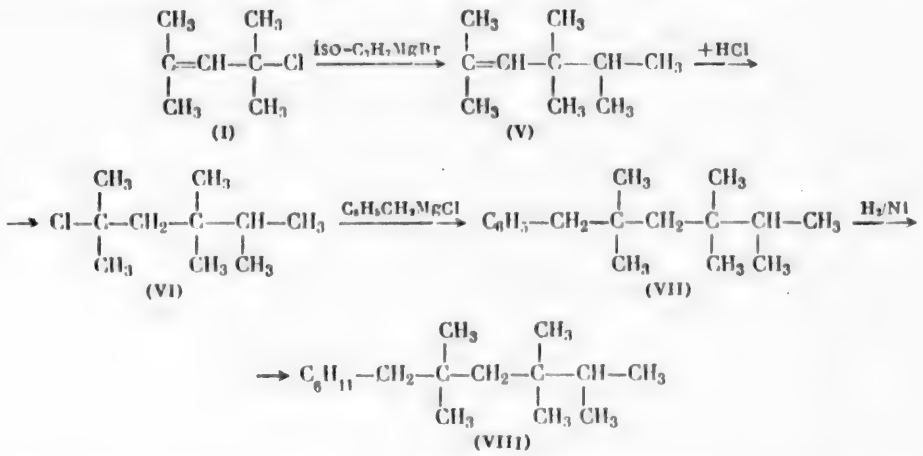


R = CH_3 and C_2H_5; R' = iso-C_3H_7.

With this procedure, employing the Grignard–Wurtz reaction twice, we synthesized 2,3,3,5-tetramethyl-5-cyclohexylhexane and 2,3,5-trimethyl-3-ethyl-5-cyclohexylheptane, in which one of the quaternary carbon atoms in the side chain was linked to a cyclohexyl radical.

Next we synthesized the cyclohexane hydrocarbon (VIII), close in its structure to the above indicated (IV), but differing from them in that a CH_2 group is found between the quaternary carbon atom of the side chain and the cyclohexyl radical. In essence, this hydrocarbon was also synthesized by the above indicated scheme, but here isopropylmagnesium bromide was used in the first Grignard–Wurtz reaction (reaction with tertiary allyl

chloride I, where R = CH_3), and benzylmagnesium chloride was used in the second (reaction with the saturated tertiary chloride VI); the obtained aromatic hydrocarbon (VII; 2,3,3,5,5-pentamethyl-6-phenylhexane) was converted by catalytic hydrogenation to the corresponding cyclohexane derivative (VIII).



It is interesting to mention that the synthesized pentamethylcyclohexylhexane ($C_{17}H_{34}$) has a much lower density than the tetramethylcyclohexylhexane ($C_{16}H_{32}$), in which the cyclohexyl group is linked directly to the quaternary carbon atom of the side chain.

EXPERIMENTAL

2,3,3,5-Tetramethyl-5-cyclohexylhexane and 2,3,5-trimethyl-3-ethyl-5-cyclohexylheptane. The hydrochlorination of 2,4-dimethyl-1,3-pentadiene (b.p. 93-94° at 755 mm, $n^{20}D$ 1.4449, d^{20}_4 0.7379) and of 3,5-dimethyl-2,4-heptadiene (in a mixture [8] with the isomeric 4-methyl-2-ethyl-1,3-hexadiene; b.p. 135-141° at 745 mm, $n^{20}D$ 1.4498, d^{20}_4 0.7679), and the reaction of the obtained allyl chlorides (I) with cyclohexylmagnesium chloride, were both carried out under the earlier described conditions [2, 4]. Synthesized in yields of 40-45% based on the starting diene, the alkenylcyclohexanes (II) had the following constants.

2,4-Dimethyl-2-cyclohexyl-3-pentene (II; R = CH_3), b.p. 98-99° (14 mm), $n^{20}D$ 1.4762, d^{20}_4 0.8542.

Literature data [7]: b.p. 101-102° (16 mm), $n^{20}D$ 1.4770, d^{20}_4 0.8550.

3,5-Dimethyl-3-cyclohexyl-4-heptene (II; R = C_2H_5), b.p. 135-136° (20 mm), $n^{20}D$ 1.4791, d^{20}_4 0.8663.

Literature data [8]: b.p. 97-97.5° (1.5 mm), $n^{20}D$ 1.4790, d^{20}_4 0.8660.

The hydrochlorination of the alkenylcyclohexanes and the reaction of the obtained saturated tertiary chlorides (III) with isopropylmagnesium bromide (in the presence of mercuric chloride) were also carried out by earlier described procedures [2-4]. The thus synthesized 2,3,3,5-tetramethyl-5-cyclohexylhexane and 2,3,5-trimethyl-3-ethyl-5-cyclohexylheptane (IV) were distilled through a column (20 theoretical plates) and then chromatographed on silica gel; their constants, the analysis data, and the yields (based on starting alkenylcyclohexane) are all given in the table. The much lower boiling starting alkenylcyclohexanes (II), appearing in the first fraction, were recycled.

2,3,3,5,5-Pentamethyl-6-phenylhexane and 2,3,3,5,5-pentamethyl-6-cyclohexylhexane. The starting 2,3,3,5-tetramethyl-4-hexene (V; b.p. 152-153° at 750 mm, $n^{20}D$ 1.4383, d^{20}_4 0.7678) was hydrochlorinated using our earlier adopted conditions [3], and the obtained saturated tertiary chloride (VI; 2-chloro-2,4,4,5-tetramethylhexane) was reacted with benzylmagnesium chloride in n-heptane medium using the method described in [1].*

*According to the data of these authors, the yield of product is increased substantially if the Grignard–Wurtz reaction of saturated tertiary chlorides with benzylmagnesium chloride is run in heptane.

Hydrocarbons of General Structure: R′—C(R)(CH$_3$)—CH$_2$—C(R)(CH$_3$)—CH(CH$_3$)—CH$_3$

Empirical formula	R′	R	Name*	Boiling point (pressure in mm)	Freezing point	n_D^{20}	d_4^{20}	MR_D found	MR_D calc.	MR_D calc.**	ν^{20} cs	Found (%) C	Found (%) H	Calc. (%) C	Calc. (%) H	Yield (%)
$C_{16}H_{32}$	C_6H_{11}	CH_3	2,3,3,5-Tetramethyl-5-cyclohexylhexane	103—104° (4)	—60° glass	1.4752	0.8615	73.34	73.89	73.30	13.2	85.63, 85.76	14.44, 14.26	85.64	14.36	9
$C_{17}H_{34}$	$C_6H_{11}CH_2$	CH_3	2,3,3,5,5-Pentamethyl-6-cyclohexylhexane	95—96 (2)	—70 glass	1.4720	0.8529	78.27	78.51	78.18	13.1	85.96, 86.11	14.24, 14.01	85.64	14.36	30
$C_{18}H_{36}$	C_6H_{11}	C_2H_5	2,3,5-Trimethyl-3-ethyl-5-cyclohexylheptane	135—135.5 (3)	—40 glass	1.4832	0.8791	82.09	83.12	82.08	43.7	85.63, 85.80	14.51, 14.30	85.64	14.36	7
$C_{17}H_{28}$	$C_6H_5CH_2$	CH_3	2,3,3,5,5-Pentamethyl-6-phenylhexane	92—93 (1)	—60 glass	1.5025	0.8901	77.10	77.11	—	12.8	87.81, 87.77	12.16, 12.15	87.87	12.13	34

*Not described in the literature.

**Using the scheme of V. M. Tatevskii [9].

The ether was distilled from the ether solution of benzylmagnesium chloride (36.5 g of Mg, 190 g of benzyl chloride, 700 ml of ether) by heating to 55°, after which the residue was kept at the same temperature in vacuo (30 mm) for 1 hr. The residue, after cooling in a stream of nitrogen, was treated with 600 ml of dry heptane and then, with vigorous stirring, 0.5 mole of the tertiary chloride was added at such a rate that the temperature of the reaction mixture remained between 30 and 35°. The next day the reaction mixture was heated for 12 hr at 30-35°, and then decomposed with dilute hydrochloric acid. Distillation of the reaction products (after the usual workup) from sodium gave a hydrocarbon fraction with b.p. 160-170° at 40 mm, from which bibenzyl was isolated by freezing, while the liquid aromatic hydrocarbon (2,3,3,5,5-pentamethyl-6-phenylhexane) was fractionated through a column (20 theoretical plates); then the latter was hydrogenated at 170-180°, using nickel deposited on aluminum oxide as the catalyst. The obtained 2,3,3,5,5-pentamethyl-6-cyclohexylhexane was fractionated through the same column (20 theoretical plates). The constants, analysis data, and yields (based on the starting tetramethylhexene) of the synthesized aromatic and cyclohexane hydrocarbons are all given in the table.

As we had mentioned earlier [3-5], the found molecular refractions (MR_D) in the case of highly branched alkanes are quite different from the calculated, when the calculation is made in the usual manner (from the atomic refractions). From the data given in the table it is obvious that the same phenomenon also exists in the case of cyclohexane hydrocarbons with a highly branched side chain; for this reason we have also given in the table the MR_D values calculated using the Tatevskii scheme [9], where the subtypes of chemical bonding are taken into account. The molecular refractions of cyclohexane hydrocarbons with two quaternary carbon atoms in the side chain, when calculated using this scheme, are in good agreement with our experimental data.

The cyclohexane hydrocarbons synthesized by us were investigated by the Raman spectral method;* the spectra showed intense frequencies in the 690, 718 and 1200-1270 cm^{-1} regions, characteristic for hydrocarbons with quaternary

*We wish to thank E. G. Treshchova for making the optical study.

carbon atoms [10], and did not show any frequencies in the 1600-1680 cm^{-1} region, which indicated the absence of unsaturated hydrocarbons as impurities.

SUMMARY

1. The general method developed by us earlier for the synthesis of alkanes with two quaternary carbon atoms, separated by a methylene group (di-tert-alkylmethanes), was extended to the synthesis of alkylcyclohexanes and alkylbenzenes, containing in the side chain an alkyl group with the same type of branching.

2. With this method we synthesized the previously unknown 2,3,3,5-tetramethyl-5-cyclohexylhexane, 2,3,5-trimethyl-3-ethyl-5-cyclohexylheptane, and 2,3,3,5,5-pentamethyl-6-phenylhexane. Hydrogenation of the latter gave us 2,3,3,5,5-pentamethyl-6-cyclohexylhexane.

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•Original Russian pagination. See C. B. translation.

δ-LACTONES AND δ-LACTAMS

XXI. DIBROMIDES OF δ-ENOLLACTAMS (5,6-DIBROMO-5,6-DIALKYL-2-PIPERIDONES)

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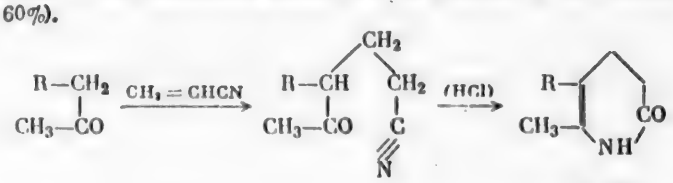
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1762-1769, June, 1960
Original article submitted June 26, 1959

Earlier we had shown that the dibromides of δ-enollactones are extremely reactive compounds, which are easily converted to 2-pyrones [1, 2], γ-bromo-δ-oxo acids, and the esters of the latter [3].

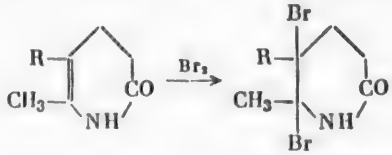
In this paper we studied some of the reactions of the dibromides of δ-enollactams (3,4-dihydro-2-pyridones), being the nitrogen analogs of the dibromides of δ-enollactones. The starting δ-enollactams were obtained by the cyclization of the nitriles of δ-oxo acid using hydrogen chloride [4]. This reaction, in which we used the monocyanoethylated methyl ketones (methyl ethyl, methyl butyl, methyl isobutyl and methyl amyl ketones) as the starting δ-oxo nitriles, proved to be a convenient method for the synthesis of 5,6-dialkyl-δ-enollactams (the yields ranged from 25 to 60%).



(I–IV)

R = CH_3, C_2H_5, iso-C_5H_{11}, C_6H_5.

The structure of the δ-enollactams (I-IV) synthesized by us in this manner is supported by the fact that their constants coincide with the constants of the δ-enollactams obtained by us earlier by a different procedure, namely, from the corresponding δ-enollactones [5]. The δ-enollactams readily added bromine in the cold to yield 5,6-dibromo-2-piperidones.*



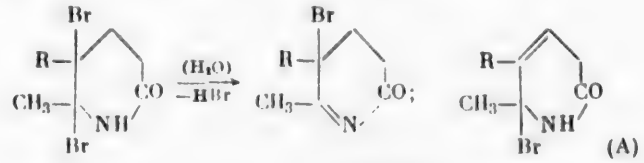
R = CH_3, C_2H_5, iso-C_5H_{11}, C_6H_5.

The δ-enollactam dibromides (5,6-dibromo-2-piperidones) cleave hydrogen bromide on standing, but at a much slower rate than the corresponding δ-enollactone dibromides [1].

By selecting the proper conditions we were able to effect the stepwise cleavage of two moles of hydrogen bromide from the 5,6-dibromo-2-piperidones.

*It could be expected that bromine not only adds to the double bond of δ-enollactams, but that it also replaces the hydrogen on the nitrogen. However, the obtained compounds failed to oxidize aqueous potassium iodide solution, which is characteristic for bromoamides.

Treating the 5,6-dibromo-2-piperidones with water (in the cold) leads to the cleavage of one mole of hydrogen bromide and the formation of 5-bromo-Δ^6-dihydro-2-pyridones.•

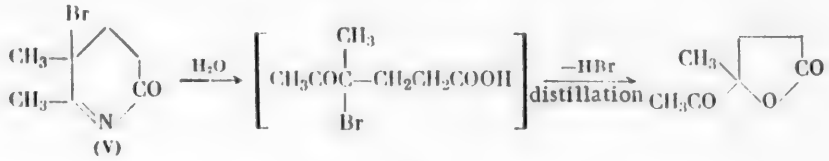


(V–VIII)

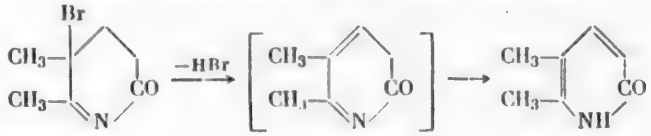
R = CH_3, C_2H_5, iso-C_3H_7, C_4H_9.

The reaction is ended in 0.5-1 hr; the yield of the monobromides (V-VIII) is 65-80%. Under these conditions the cleavage of one mole of hydrogen bromide from the dibromides could also proceed in a different manner•• with the formation of the isomeric unsaturated monobromide having the bromide atom in the 6 position (A). However, the first manner of hydrogen bromide cleavage is the more probable, since we had shown earlier [3] that in the corresponding 5,6-dibromolactones the bromine atom in the 6 position is considerably more labile.

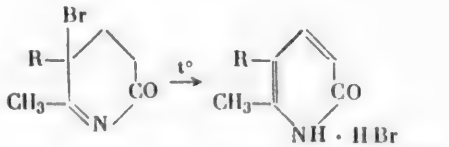
The structure of the synthesized monobromides as being 5-bromo-Δ^6-dihydro-2-pyridones was confirmed on the example of monobromide (V), since the hydrolysis (heating with water) of this compound, followed by distillation, gave 5-methyl-5-acetylbutyrolactone,••• the formation of which could occur only if the monobromide (V) had the bromine atom in the 5 position.



Together with the butyrolactone, the corresponding 2-pyridone is also formed.



5-Bromo-5,6-dialkyl-Δ^6-dihydro-2-pyridones, possessing a labile bromine atom, are extremely reactive compounds. When distilled in vacuo they undergo a peculiar rearrangement to the hydrobromides of the corresponding 2-pyridones in 40-50% yield.



(IX–XI)

R = C_3H_7, iso-C_3H_7, C_4H_9.

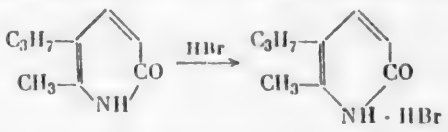
Using 5-bromo-6-methyl-5-butyl-Δ^6-dihydro-2-pyridone as an example, it was shown that the same isomerization also takes place if a xylene solution of the compound is refluxed. The pyridone hydrobromides formed in this manner, being isomeric with the starting monobromides, differ sharply from the latter in both melting point and chemical properties; they are hydrolyzed with extreme ease by water, converting to 5,6-dialkyl-2-pyridones.

•In contrast to the δ-enollactone dibromides, which react with water with opening of the ring and the formation of γ-bromo-δ-oxo acids [3].

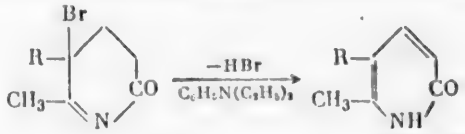
••The cleavage of hydrogen bromide in the side chain with the formation of monobromides having semicyclic position of the double bond apparently does not take place, since the monobromides (V-VIII) are easily converted to the corresponding 2-pyridones when reacted with diethylaniline (see later).

•••We had previously synthesized 5-methyl-5-acetylbutyrolactone from γ-bromo-γ-acetylvaleric acid [6].

The structure of pyridone hydrobromides (IX–XI) was confirmed by the counter synthesis of one of them (IX), by the reaction of gaseous hydrogen bromide with the appropriate pyridone.



The 5-bromo-5,6-dialkyl-Δ^6-dihydro-2-pyridones when reacted with diethylaniline cleave hydrogen bromide to form the corresponding 5,6-dialkylpyridones (XII–XV) in 10-45% yield.

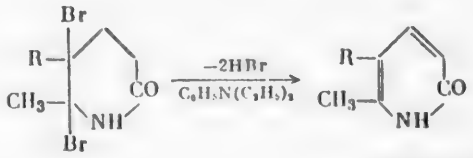


(XII–XV)

R = CH_3, C_3H_7, iso-C_3H_7, C_4H_9.

This same reaction also takes place when the monobromides (V–VIII) are heated with water; the yield of the pyridones in this case is 15%. The structure of the obtained 2-pyridones was confirmed on the example of 5,6-dimethyl-2-pyridone (XII), the constants of which coincide with those given in the literature [7, 8], and also by the counter synthesis of 6-methyl-5-propyl-2-pyridone (XIII) from the corresponding 2-pyrone.

We also obtained the 5,6-dialkyl-2-pyridones by reacting the 5,6-dibromo-2-piperidones with diethylaniline; the simultaneous cleavage of two moles of hydrogen bromide occurs here, and the dialkyl-2-pyridones are formed in 20-23% yield.



(XIII–XV)

R = C_3H_7, iso-C_3H_7, C_4H_9.

As a result, the 5,6-dibromo-5,6-dialkyl-2-piperidones (dibromides of δ-enollactams) easily cleave hydrogen bromide, being converted to the difficultly available 5,6-dialkyl-2-pyridones; the cleavage of two moles of hydrogen bromide can be carried out either at once to the 5,6-dialkyl-2-pyridones or in stages with the intermediate formation of the reactive monobromides—the 5-bromo-5,6-dialkyl-Δ^6-dihydro-2-pyridones.

EXPERIMENTAL

The monocyanoethylated methyl alkyl ketones (δ-oxo nitriles) were obtained by methods described by us earlier [5, 9].

5,6-Dialkyl-3,4-dihydro-2-pyridones (cyclization of δ-oxo nitriles). A stream of dry hydrogen chloride was passed into a solution of 0.5 mole of the δ-oxo nitrile in 100 ml of chloroform until saturated. The reaction mixture was allowed to stand at room temperature for 4 hr, after which the solvent was distilled off and the residue was vacuum-distilled. The crystals of dihydropyridone that separated from the distillate were filtered and washed on the filter with petroleum ether (acetone was used for this purpose in the case of 5,6-dimethyl-3,4-dihydro-2-pyridone). The melting points (after recrystallization), yields and literature data for the obtained 3,4-dihydro-2-pyridones (δ-enollactams) are given in Table 1.

5,6-Dibromo-5,6-dialkyl-2-piperidones. With cooling and vigorous stirring, a solution of 0.1 mole of bromine in 10 ml of chloroform was added in drops to a solution of 0.1 mole of 3,4-dihydro-2-pyridone in 50-60 ml of chloroform. The solvent was evaporated in vacuo. The residue was either a crystalline substance, or a thick oil that crystallized when rubbed. The melting points of the dibromopiperidones (after recrystallization from benzene) are given in Table 1. The dibromides were not analyzed, since they cleaved hydrogen bromide with ease.

TABLE 1

5,6-Dialkyl-3,4-dihydro-2-pyridones and their Dibromides

Compound No.	Name	Melting point	Yield (%)	Found (%)		Formula	Calculated (%)		Melting point of dibromide
				C	H		C	H	
(I)	5,6-Dimethyl-3,4-dihydro-2-pyridone	125-126° (from ethyl acetate)	54	67.36 67.46	8.91 8.96	$C_7H_{11}ON$	67.20	8.81	–
(II)	6-Methyl-5-propyl-3,4-dihydro-2-pyridone	67.69• (from ether)	36	–	–	–	–	–	70-72° (from benzene)
(III)	6-Methyl-5-isopropyl-3,4-dihydro-2-pyridone	99-100 (from petroleum ether)	25	70.60 70.49	9.94 9.95	$C_9H_{15}ON$	70.59	9.80	79-80 (from benzene)
(IV)	6-Methyl-5-butyl-3,4-dihydro-2-pyridone	58•• (from petroleum ether)	60	–	–	–	–	–	69-71 (from benzene

•From the literature [5]: m.p. 68-70°.

••From the literature [5]: m.p. 57-58°.

5-Bromo-5,6-dialkyl-Δ^6-dihydro-2-pyridones (V–VIII). With vigorous stirring, 0.01 mole of the 5,6-dibromo-2-piperidone (obtained as described above) was treated with 15-20 ml of cold water. Here the dibromide first changed to a thick oil, which crystallized after stirring for 30-40 min. The melting points (after recrystallization from petroleum ether), yields and analysis data for the obtained bromohydropyridones (V–VIII) are given in Table 2.

To prove the structure of the obtained 5-bromodihydro-2-pyridones we hydrolyzed 5-bromo-5,6-dimethyl-Δ^6-dihydro-2-pyridone (V). A solution of 3 g of (V) in 8 ml of dilute (2 : 1) hydrochloric acid was refluxed for 1 hr, then diluted with an equal volume of water and extracted 5 times with ether. After evaporation of the solvent and vacuum-distillation of the residue we obtained a substance with b.p. 135-140° at 50 mm and $n^{20}D$ 1.4620, which readily gave a semicarbazone with m.p. 178-179° (from alcohol); the mixed melting point with authentic 5-methyl-5-acetylbutyrolactone semicarbazone was not depressed.

Literature data for 5-methyl-5-acetylbutyrolactone: b.p. 119° at 13 mm, $n^{20}D$ 1.4600; semicarbazone: m.p. 180° [6].

Neutralization of the hydrochloric acid solution from the ether extraction with potassium carbonate gave a precipitate of 5,6-dimethyl-2-pyridone (XII). Weight 0.26 g (15% yield), m.p. 205-206° (from acetone).

5,6-Dialkyl-2-pyridone hydrobromides (IX–XI) (Isomerization of 5-bromo-5,6-dialkyldihydro-2-pyridones). The bromodihydropyridone (0.01 mole) was heated in vacuo at 40-50 mm for 10-15 min, and then it was distilled. The obtained distillate crystallized on standing. The melting points (after recrystallization), yields and analysis data are given in Table 3.

6-Methyl-5-butyl-2-pyridone hydrobromide was also obtained by heating bromide (VIII) (1 g) in xylene (6 ml) solution for 15 min; hydrogen bromide was evolved here; the solution on cooling deposited crystals with m.p. 184-187° (from acetone), which failed to depress the melting point when mixed with the 6-methyl-5-butyl-2-pyridone obtained by the distillation of bromide (VIII).

The 2-pyridone hydrobromides are readily soluble in water; the corresponding 2-pyridones separate from the solution when ammonia is added.

The structure of the pyridone hydrobromides (IX–XI) was shown by the counter synthesis of one of them, namely, 6-methyl-5-propyl-2-pyridone hydrobromide (IX). A solution of 0.2 g of 6 methyl-5-propyl-2-pyridone in 2 ml of dry benzene was saturated with dry gaseous hydrogen bromide. Here a precipitate deposited from the

TABLE 2

5-Bromo-5,6-dialkyl-Δ^6-dihydro-2-pyridones

Compound No	Name	Melting point (from petroleum ether)	Yield(%)	Found (%)		Formula	Calc. (%)	
				C	H		C	H
(V)	5-Bromo-5,6-dimethyl-Δ^6-dihydro-2-pyridone	91—93° (benzene)	65	41.28, 41.48	4.92, 5.07	$C_7H_{10}ONBr$	41.17	4.85
(VI)	5-Bromo-6-methyl-5-propyl-Δ^6-dihydro-2-pyridone	113—114	80	46.93, 46.75	6.15, 6.23	$C_9H_{14}ONBr$	46.55	6.03
(VII)	5-Bromo-6-methyl-5-isopropyl-Δ^6-dihydro-2-pyridone	107—108	73	46.64, 46.61	6.22, 6.17	$C_9H_{14}ONBr$	46.55	6.03
(VIII)	5-Bromo-6-methyl-5-butyl-Δ^6-dihydro-2-pyridone	108—109*	68	49.28, 49.08	6.46, 6.43	$C_{10}H_{16}ONBr$	48.78	6.50

*First melts at 108-109°, then it solidifies and melts again at 170-175° (i.e., on melting it isomerizes almost completely to the pyridone hydrobromide—see below).

TABLE 3

5,6-Dialkyl-2-pyridone Hydrobromides

Compound No	Name	Melting point	Yield(%)	Found (%)		Formula	Calc. (%)	
				C	H		C	H
(IX)	6-Methyl-5-propyl-2-pyridone hydrobromide	153—155° (from ethyl acetate)	50	46.15, 46.17	6.09, 5.99	$C_9H_{14}ONBr$	46.55	6.03
(X)	6-Methyl-5-isopropyl-2-pyridone hydrobromide	177—178 (from acetone)	48	46.83, 46.93	6.24, 6.13	$C_9H_{14}ONBr$	46.55	6.03
(XI)	6-Methyl-5-butyl-2-pyridone hydrobromide	185—187 (from acetone)	48	48.94, 48.69	6.65, 6.57	$C_{10}H_{16}ONBr$	48.78	6.50

solution, which was filtered and recrystallized from ethyl acetate; m.p. 152-154° (yield 50%). The mixed melting point with the hydrobromide (IX) obtained by the distillation of 5-bromo-6-methyl-5-propyl-Δ^6-dihydro-2-pyridone was not depressed.

5,6-Dialkyl-2-pyridones (XII—XV) from 5-bromo-5,6-dialkyl-Δ^6-dihydro-2-pyridones. a) Cleavage of hydrogen bromide by heating with diethylaniline. A mixture of 0.01 mole of the bromodihydropyridone and 0.01 mole of diethylaniline was heated at 150-160° for 10 min, after which the mixture was cooled, dissolved in 8 ml of water, and the solution was neutralized with aqueous ammonia solution. Here the pyridone was obtained as a precipitate, which was dried first in the air, and then at 50-60°. The melting points (after recrystallization*), analysis data and yields of the obtained pyridones (XII—XV) are given in Table 4.

b) Cleavage of hydrogen bromide by refluxing with water. A mixture of 0.01 mole of the bromodihydropyridone and 5 ml of water was refluxed for 15 min, after which the solution was neutralized with aqueous ammonia solution. The pyridone came out of solution on cooling. After filtration and drying at 50-60°, the melting point was determined. The yields of the 2-pyridones obtained in this manner are given in Table 4.

*The synthesized pyridones recrystallize well from water, but here they are found to contain water of crystallization, which is easily removed by drying at 60°.

TABLE 4

5,6-Dialkyl-2-pyridones

Compound No.	Name	Melting point	Found (%)		Formula	Calculated (%)		Yield (%)		
			C	H		C	H	from bromodihydropyridone and		from dibromopiperidone and
								$C_5H_5N(C_2H_5)_2$	H_2O	$C_5H_5N(C_2H_5)_2$
(XII)	5,6-Dimethyl-2-pyridone	205—206° * (from acetone)	68.38, 68.33	7.57, 7.67	C_7H_9ON	68.29	7.31	10	15	—
(XIII)	6-Methyl-5-propyl-2-pyridone	129—130 (from acetone	71.37, 71.59	8.60, 8.38	$C_9H_{13}ON$	71.52	8.60	25	15	23
(XIV)	6-Methyl-5-isopropyl-2-pyridone	171—171.5 (from petroleum ether)	71.60, 71.64	8.62, 8.80	$C_9H_{13}ON$	71.52	8.60	25	17	20
(XV)	6-Methyl-5-butyl-2-pyridone	92—93 (from petroleum ether)	72.30, 72.38	9.04, 9.15	$C_{10}H_{15}ON$	72.72	9.09	45	15	23

*Literature data: m.p. 205-206° [7]; 208-209° [8].

To prove the structure of the synthesized 2-pyridones we carried out the counter synthesis of 6-methyl-5-propyl-2-pyridone. A mixture of 0.65 g of 6-methyl-5-propyl-2-pyrone* (b.p. 121-122° at 16 mm, $n^{20}D$ 1.5170), 2 g of ammonium acetate and 0.7 g of glacial acetic acid was refluxed for 9 hr, after which 2 ml of water and 1 ml of concd. aqueous ammonia solution were added to the reaction mixture. An oil separated from the solution, which crystallized on standing. Recrystallization from petroleum ether gave 6-methyl-5-propyl-2-pyridone with m.p. 127-128°; the mixed melting point with the pyridone obtained from 5-bromo-6-methyl-5-propyl-Δ^6-dihydro-2-pyridone was not depressed.

5,6-Dialkyl-2-pyridones from 5,6-dibromo-2-piperidones. A mixture of 0.05 mole of the 5,6-dibromo-2-piperidone and 0.1 mole of diethylaniline was heated for 5-10 min at 150-160° until all of the dibromide had dissolved. Then the mixture was dissolved in 5-10 ml of hot water and the obtained solution was treated with aqueous ammonia solution until neutral. The obtained crystalline pyridone was filtered and dried at 50-60°. The yields of the pyridones (XIII--XV) obtained in this manner are given in Table 4.

We were unable to obtain 5,6-dimethyl-2-pyridone (XII) in this manner.

SUMMARY

1. The cyclization of δ-oxo nitriles gave 5,6-dialkyl-3,4-dihydro-2-pyridones in 25-60% yields.

2. 5,6-Dialkyl-3,4-dihydro-2-pyridones add bromine at the double bond with the formation of 5,6-dibromo-5,6-dialkyl-2-piperidones.

3. 5,6-Dibromo-2-piperidones when treated with water in the cold cleave one mole of hydrogen bromide and are converted to 5-bromo-Δ^6-dihydro-2-pyridones in 66-80% yields.

4. The 5-bromo-Δ^6-dihydro-2-pyridones isomerize to the corresponding 2-pyridone hydrobromides when distilled.

5. 5-Bromo-5,6-dialkyl-Δ^6-dihydro-2-pyridones are converted to 5,6-dialkyl-2-pyridones in 10-45% yield when treated with either diethylaniline or water.

6. The reaction of diethylaniline with 5,6-dibromo-5,6-dialkyl-2-piperidones also gives 5,6-dialkyl-2-pyridones in 20-23% yield.

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*Synthesized by our earlier described method [2] from 6-methyl-5-propyl-δ-enollactone dibromide.

••Original Russian pagination. See C. B. translation.

PROPERTIES OF $C_{14}-C_{28}$ NAPHTHENE HYDROCARBONS OF VARIABLE STRUCTURE

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1769-1780, June, 1960
Original article submitted June 7, 1959

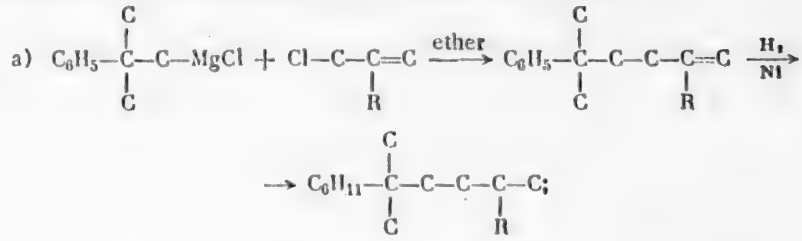
A study of the properties of individual hydrocarbons of variable structure and composition makes it possible to validly appraise the possibility of the practical utilization of hydrocarbons differing among themselves in their type of structure. In addition, such studies are needed to establish the structure of the high-molecular hydrocarbons of natural petroleums, which, without doubt, will help in throwing some light on the origin and genesis of petroleums.

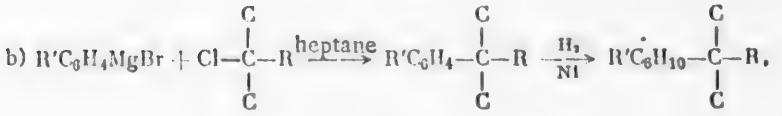
For hydrocarbons, especially the naphthenes, the greatest interest is possessed by such properties as the boiling point, freezing point, density, heat of combustion, and viscosity. At the present time the use of these properties has made possible a quite adequate characterization of alkanes [1, 2], lower alkylbenzenes [1-4], 2-alkylbiphenyls [5] and 1-alkylnaphthalenes [6], phenylalkanes with a straight chain [1, 2], p-benzylalkylbenzenes [7], and the simpler polycyclic aromatic hydrocarbons [3, 4, 8]. Among the naphthene hydrocarbons, the heat capacity and a number of other physical properties were determined for the simpler alkylcyclopentanes [1, 2] and alkylcyclohexanes [1-3], cyclohexylalkanes with a straight chain [1, 2], dicyclohexylalkanes of various structure types [9-11], a number of isomeric o-cyclohexylalkylcyclohexanes [12], and the cis- and trans-decalins [13]. Most of these investigations were carried out by Wise and co-workers in 1950-1954 and by Parks and coworkers in 1930-1940. Quite recently [14] some data were presented on the net gravimetric and volumetric heats of combustion of the paraffin, naphthene and aromatic hydrocarbons isolated chromatographically from the narrow fractions of petroleum products. Here it proved that the naphthene hydrocarbons had the greatest volumetric heat capacity.

As a result, it is obvious that up to now studies of this type have been limited to the acyclic, the simpler alicyclic, and the aromatic hydrocarbons. Data on the more important physical properties of the individual $C_{14}-C_{20}$ alkylcyclohexanes with a branched side chain, the alkyldecalins, and even more so, on the tricyclohexylalkanes and didecalylalkanes, are completely absent in the literature.

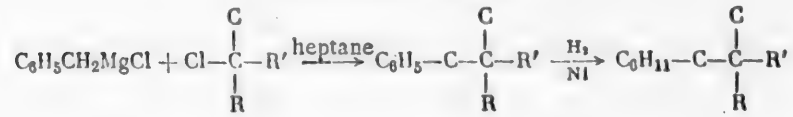
In the present paper we made an attempt to establish the dependence of the net gravimetric and volumetric heats of combustion and a number of other properties of naphthene hydrocarbons of the indicated structure types on their molecular weight and structure, and first of all the dependence of these properties on the number and mutual arrangement of the naphthene rings in the molecule, and also on the degree of branching of the side chain. For this purpose, employing the technique of catalytic hydrogenation of various individual alkylaromatic hydrocarbons of the benzene and naphthalene series, first synthesized by us through the organomagnesium and organolithium compounds, we obtained some naphthene hydrocarbons with the following main types of structures.

1) Alkylcyclohexanes with a quaternary carbon atom in the side chain:

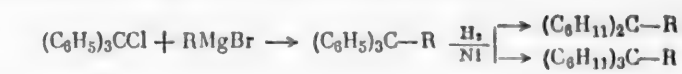




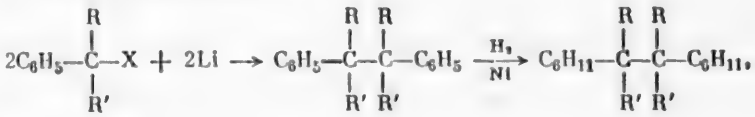
where R′ = H or CH_3;



2) 1,1-Dicyclohexylalkanes and 1,1,1-tricyclohexylalkanes:



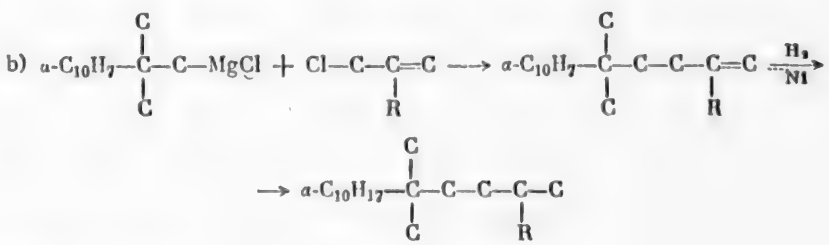
3) Substituted 1,2-dicyclohexylethanes:



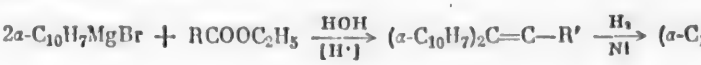
where X = Cl or Br, and R = H or CH_3.

4) α-Alkyldecalins:

where X = Cl or Br;



5) 1,1-Di-(α-decalyl)-alkanes:



In addition to the hydrocarbons of the indicated types, we synthesized a number of isoparaffin hydrocarbons of composition C_{12}–C_{22} [15] employing the Wurtz and Grignard reactions, and also some di- and tricyclohexylalkanes with the cyclohexyl rings attached in different places along the chain.

The net heat capacity, and also the freezing (melting) points, density, and kinematic viscosity at 20° of the obtained paraffin and naphthene hydrocarbons, arranged in the order of increasing number of rings and

molecular weight, are given in the table. The details of the synthesis of most of the starting alkylaromatic hydrocarbons, their hydrogenation, and also some of the properties of these compounds (boiling points, freezing, points, density, kinematic viscosity at 0-200°) were described by us earlier [16-18].

From the data given in the table it can be seen that the naphthene hydrocarbons with the highest hydrogen content, as was to be expected, had the highest gravimetric heat of combustion (10,420-10,705 kcal/kg). In addition, these hydrocarbons (with the exception of 11-methyleneicosane) had low freezing points (from -80° to -115°) and a low viscosity (1.5-8 centistokes at 20°). However, because of the comparatively low density (0.753-0.794) the volumetric heat of combustion of the given alkanes, as is in general true of most paraffin hydrocarbons, was small and constituted a total of only 8060-8330 kcal/liter.

A substantial increase in the density occurred on going from the acyclic hydrocarbons to the monocyclic and, especially, to the bicyclic naphthene hydrocarbons of the cyclohexane series. Here the density went up to 0.823-0.844 for alkylcyclohexanes of composition C_{13}—C_{20} and up to 0.869-0.927 for dicyclohexylalkanes of composition C_{17}—C_{27}, which, despite the lower gravimetric heat capacity of these hydrocarbons (10,230-10,420 kcal/kg), gave a noticeable increase in the volumetric heat capacity, respectively equal to 8545-8760 and 8975-9565 kcal/liter. The bicyclic naphthenes with condensed rings—the α-alkyldecalins of composition C_{17}—C_{18}—had a net gravimetric heat capacity of 10,240-10,315 kcal/kg with a density of 0.869-0.886 kg/liter, which corresponded to a volumetric heat capacity of 8925-9140 kcal/liter, i.e., the alkyldecalins occupy a middle position between the mono and dicyclohexylalkanes of the same composition. The low freezing points of the alkylcyclohexanes (from -57 to -114°) and of the alkyldecalins (from -55 to -70°), and their comparatively low viscosity, respectively 3-10 and 11-25 centistokes at 20°, should also be mentioned here as being a beneficial factor. The naphthenes with three rings—the tricyclohexylalkanes of composition C_{25}—C_{29}—had an even higher density (d^{40}_4 0.900-0.934), and consequently, an even higher volumetric heat of combustion (9255-9635 kcal/liter). However, the latter, the same as the dicyclohexylalkanes, solidified at temperatures ranging from -25 to 10°, and had a viscosity of 50-635 centistokes at 20-50°.

Further increase in the number of rings in the hydrocarbons, and specifically, transition to the tetracyclic naphthenes—the didecalylalkanes, having the highest specific gravity of all of the hydrocarbons investigated (0.952-0.977)—gave an increase in the volumetric heat capacity up to 9665-9850 kcal/liter, although their gravimetric heat capacity was only 10,080-10,150 kcal/kg. The highest volumetric heat of combustion—9995 kcal/liter—was possessed by 1,1-di-(α-tetralyl)-ethane, in which the total hydrogen content was only 9.14%, but the density of which was 1.057 kg/liter. The high freezing points (5-25°) and the enormous viscosity (400-950 centistokes at 50°) were also a serious disadvantage of these hydrocarbons. However, these characteristics can be corrected by mixing the latter with lighter hydrocarbons, for example, with paraffin hydrocarbons. Thus, if 1,1-didecalylbutane has f.p. 18° and ν^{50} 934.8 centistokes, then a mixture of this compound with 5,8-diethyldodecane, having f.p. -92° and ν^{20} 3.5 centistokes, taken in a weight ratio of approximately 1 : 1 (46.3% naphthene and 53.7% alkane), now froze at -54° and had a kinematic viscosity of only 26.5 centistokes (20°), with a quite high volumetric and gravimetric heat of combustion (10,350 kcal/kg or 8960 kcal/liter).

As a result, among the paraffin and naphthene hydrocarbons the volumetric heat capacity increased (with a simultaneous decrease in the gravimetric heat capacity) as the number of rings in the hydrocarbons was increased, i.e., in going from the alkanes to the mono-, di-, tri- and tetracyclic cyclanes, which was due to an increase in their density. However, this increase in the volumetric heat of combustion is accompanied, as a rule, by a simultaneous impairment in the viscosity and low-temperature properties of the hydrocarbons.

In addition to the number of rings and the molecular weight, the character of the relative position of the rings in the hydrocarbon molecule, and for the alkylcyclohexanes—the extent of branching of the alkyl chain—exerts a definite influence on the properties of the naphthene hydrocarbons. Thus, among the di- and tricyclohexylalkanes examined by us a separation of the cyclohexyl rings from each other caused a sharp decrease in the freezing point, but here the density decreased correspondingly, and consequently, so did both the volumetric heat of combustion and the viscosity of these hydrocarbons. For example, the freezing points of 2-methyl-2-isobutyl-1,3-dicyclohexylpropane and 3-decyl-1,5-dicyclohexylpentane (Nos. 24 and 28 in the table), and also of 4-(cyclohexylethyl)-1,7-dicyclohexylheptane (No. 31), ranged from -50 to -25°, whereas the 1,1-di- and 1,1,1-tricyclohexylalkanes had a higher freezing point (from -5 to 10°) and a higher viscosity (up to 635 centistokes at 50°), but then they also had a higher heat capacity per unit of volume (up to 9600 kcal/liter). In a similar

TABLE

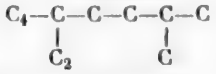
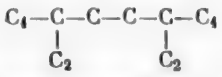
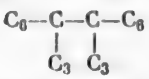
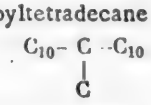
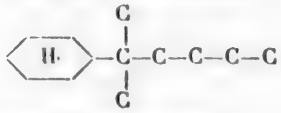
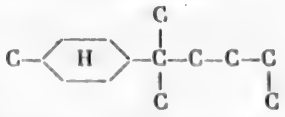
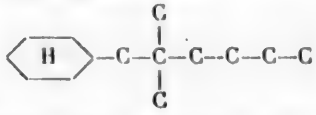
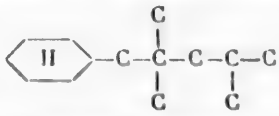
No.	Hydrocarbons	Formula	Freezing (or melting) point	d_4^{20}	ν_{20} in cc	Net heat of combustion Q_b^n in kcal/kg	Net heat of combustion Q_b^n in kcal/liter
1	2	3	4	5	6	7	8
	ALKANES						
1		$C_{12}H_{26}$	—116° (Glass)	0.7529	1.51	10705	8060
	2-Methyl-5-ethylnonane						
2		$C_{18}H_{34}$	—92 (Glass)	0.7822	3.49	10485	8200
	5,8-Diethyldodecane						
3		$C_{20}H_{42}$	—86 (Glass)	0.7942	8.07	10420	8275
	7,8-Dipropyltetradecane						
4		$C_{22}H_{46}$	+15 (Crystal)	0.7942	—	10490	8330
	11-Methylheneicosane						
	ALKYLCYCLOHEXANES						
5		$C_{13}H_{26}$	—87 (Glass)	0.8330	3.56	10300	8580
	2-Methyl-2-cyclohexane						
6		$C_{14}H_{28}$	—95 (Glass)	0.8246	3.92	10360	8545
	1-Methyl-4-(1',1',3'-trimethylbutyl)cyclohexane						
7		$C_{14}H_{28}$	—80 (Glass)	0.8262	3.86	10370	8570
	2,2-Dimethyl-1-cyclohexylhexane						
8		$C_{11}H_{28}$	—114 (Glass)	0.8233	3.27	10420	8580
	2,2,4-Trimethyl-1-cyclohexylpentane						

TABLE (Continued)

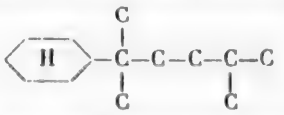
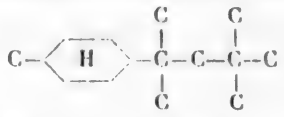
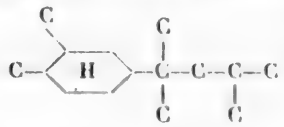
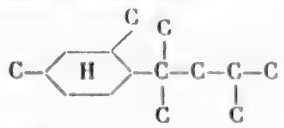
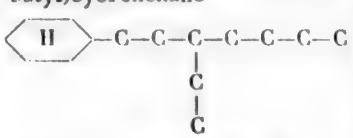
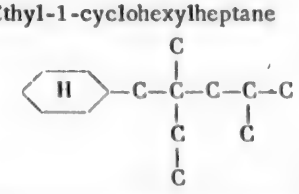
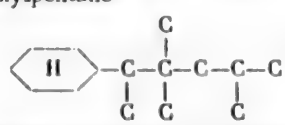
No.	Hydrocarbons	Formula	Freezing (or melting) point	d_4^{20}	ν^{20} (in cs)	Net heat of combustion Q_p^0	
						kcal/kg	in kcal/liter
1	2	3	4	5	6	7	8
9	 2,5-Dimethyl-2-cyclohexylhexane	$C_{14}H_{28}$	—83° (Glass)	0.8446	5.10	10230	8640
10	 1-Methyl-4-(1',1',3',3'-tetramethylbutyl)cyclohexane	$C_{15}H_{30}$	—72 (Glass)	0.8366	6.01	10405	8625
11	 1,2-Dimethyl-4-(1',1',3'-trimethylbutyl)cyclohexane	$C_{15}H_{30}$	—80 (Glass)	0.8321	4.38	10370	8630
12	 1,3-Dimethyl-4-(1',1',3'-trimethylbutyl)cyclohexane	$C_{15}H_{30}$	—80 (Glass)	0.8340	4.18	10385	8660
13	 3-Ethyl-1-cyclohexylheptane	$C_{15}H_{30}$	—65 (Glass)	0.8230	4.04	10380	8545
14	 2,4-Dimethyl-2-ethyl-1-cyclohexylpentane	$C_{15}H_{30}$	—76 (Glass)	0.8365	5.35	10415	8715
15	 1,2,2,4-Tetramethyl-1-cyclohexylpentane	$C_{15}H_{30}$	—84 (Glass)	0.8442	5.28	10360	8745

TABLE (Continued)

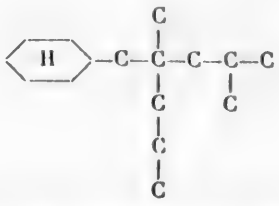
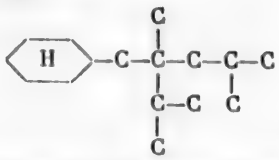
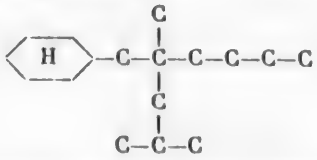
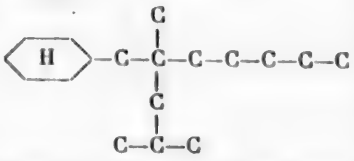
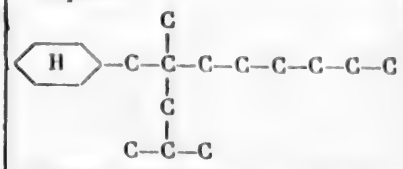
No.	Hydrocarbon	Formula	Freezing (or melting) point	d_4^{20}	ν^{20} (incs)	Net heat of combustion Q_b^n in kcal/kg	Net heat of combustion Q_b^n in kcal/liter
1	2	3	4	5	6	7	8
16	 2,4-Dimethyl-2-propyl-1-cyclohexylpentane	$C_{16}H_{32}$	−83° (Glass)	0.8368	5.45	10420	8720
17	 2,4-Dimethyl-2-isopropyl-1-cyclohexylpentane	$C_{16}H_{32}$	−78 (Glass)	0.8438	6.82	10380	8760
18	 2-Methyl-1-isobutyl-1-cyclohexylhexane	$C_{17}H_{34}$	−68 (Glass)	0.8382	9.10	10320	8650
19	 2-Methyl-2-isobutyl-1-cyclohexylheptane	$C_{18}H_{36}$	−66 (Glass)	0.8345	9.71	10355	8640
20	 2-Methyl-2-isobutyl-1-cyclohexyloctane	$C_{19}H_{38}$	−64 (Glass)	0.8303	10.38	10350	8595

TABLE (Continued)

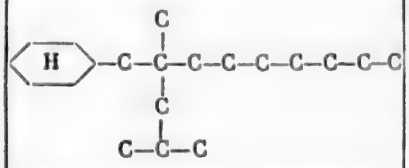
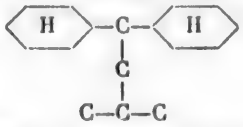
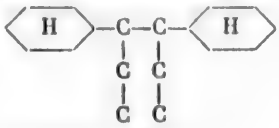
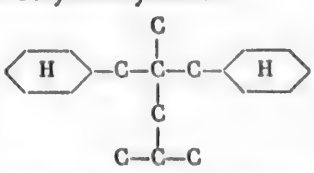
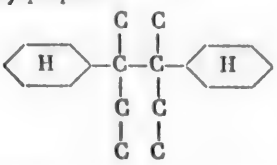
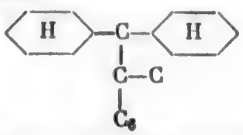
No.	Hydrocarbon	Formula	Freezing (or melting) point	d_4^{20}	ν^{20} (in cs)	Net heat of combustion Q_b^n in kcal/kg	Net heat of combustion Q_b^n in kcal/liter
1	2	3	4	5	6	7	8
21	 2-Methyl-2-isobutyl-1-cyclohexylnonane	$C_{20}H_{40}$	−57° (Glass)	0.8373	14.38	10365	8680
	DICYCLOHEXYLALKANES						
22	 3-Methyl-1,1-dicyclohexylbutane	$C_{17}H_{32}$	+8 (Crystals)	0.8885	34.7	10300	9150
23	 3,4-Dicyclohexylhexane	$C_{18}H_{34}$	−27 (Glass)	0.8962	40.11	10345	9275
24	 2-Methyl-2-isobutyl-1,3-dicyclohexylpropane	$C_{20}H_{38}$	−45 (Glass)	0.8820	47.56	10385	9160
25	 3,4-Dimethyl-3,4-dicyclohexylhexane	$C_{20}H_{38}$	−7 (Glass)	0.9270	228.3	10315	9565
26	 2-Methyl-1,1-dicyclohexyloctane	$C_{21}H_{40}$	—	0.9090	—	10280	9345

TABLE (Continued)

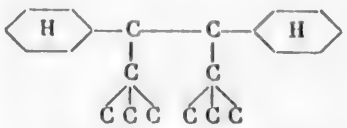
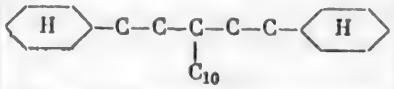
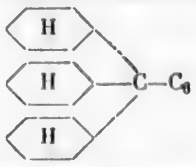
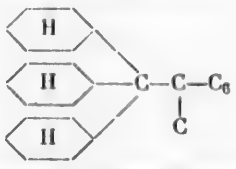
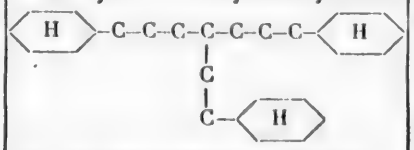
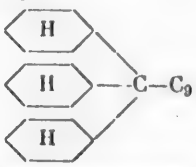
No.	Hydrocarbon	Formula	Freezing (or melting) point	d_4^{20}	ν^{20} (in cs)	Net heat of combustion Q_b^n	
						in kcal/kg	in kcal/liter
1	2	3	4	5	6	7	8
27	 2,2,5,5-Tetramethyl-3,4-dicyclohexylhexane	$C_{22}H_{42}$	−6° (Glass)	0.9020	448.0	10340	9325
28	 3-Decyl-1,5-dicyclohexylpentane	$C_{27}H_{52}$	−50 (Glass)	0.8695	47.55	10325	8975
	TRICYCLOHEXYLALKANES						
29	 1,1,1-Tricyclohexylheptane	$C_{25}H_{46}$	10 (Glass)	0.9344 (d_4^{40})	635.0 (50°)	10145	9595
30	 2-Methyl-1,1,1-tricyclohexyloctane	$C_{27}H_{50}$	2 (Glass)	0.9269 (d_4^{40})	431.0 (50°)	10265	9635
31	 4-(Cyclohexylethyl)-1,7-dicyclohexylheptane	$C_{27}H_{50}$	−25 (Glass)	0.9005 (d_4^{40})	274.6	10280	9255
32	 1,1,1-Tricyclohexyldecane	$C_{28}H_{52}$	3 (Glass)	0.9167 (d_4^{40})	133.6 (50°)	10240	9510

TABLE (Continued)

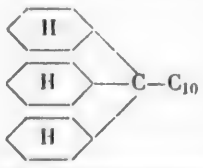
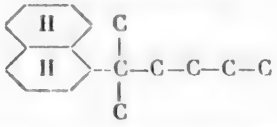
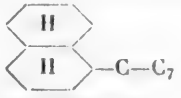
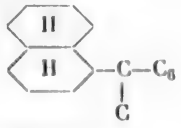
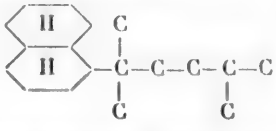
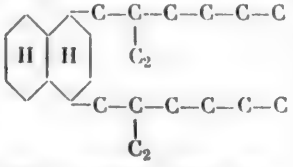
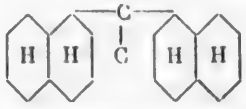
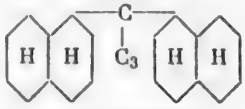
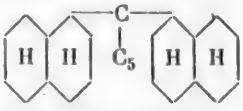
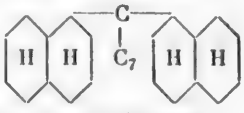
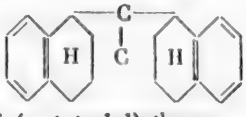
No.	Hydrocarbon	Formula	Freezing (or melting) point	d_4^{20}	ν_{20} (in cs)	Net heat of combustion Q_b^n	
						in kcal/kg	in kcal/liter
1	2	3	4	5	6	7	8
33	 1,1,1- Tricyclohexylundecane	$C_{29}H_{54}$	−5° (Glass)	0.9035 (d_4^{40})	130.0 (50°)	10290	9505
	α-ALKYLDECALINS						
34	 2-Methyl-2-(α-decalyl)hexane	$C_{17}H_{32}$	—	0.8798	21.50	10280	9045
35	 α-n-Octyldecalin	$C_{18}H_{34}$	−14.5 (Crystal)	0.8689	11.24	10270	8925
36	 α-sec-octyldecalin	$C_{18}H_{34}$	−68 (Glass)	0.8749	12.57	10240	8960
37	α-(2-Ethylhexyl)decalin	$C_{18}H_{34}$	−55.5 (Glass)	0.8739	14.38	10315	9015
38	 2,5-Dimethyl-2-(α-decalyl)hexane	$C_{18}H_{34}$	—	0.8867	25.71	10310	9140
39	 1,4-Di-(2'-ethylhexyl)decalin	$C_{26}H_{50}$	−42 (Glass)	0.8762	472.6	10340	9060

TABLE (Continued)

No.	Hydrocarbons	Formula	Freezing (or melting) point	d_4^{20}	ν^{20} (in cs)	Net heat of combustion Q_b^n in kcal/kg	Net heat of combustion Q_b^n in kcal/liter
1	2	3	4	5	6	7	8
	1,1-DI-(α-DECALYL)-ALKANES						
40	 1,1-Di-(α-decalyl)ethane	$C_{22}H_{38}$	22° (Glass)	0.9774	—	10080	9850
41	 1,1-Di-(α-decalyl)butane	$C_{24}H_{42}$	18 (Glass)	0.9620	934.8 (50°)	10120	9735
42	 1,1-Di-(α-decalyl)hexane	$C_{26}H_{46}$	10 (Glass)	0.9592	839.3 (50°)	10150	9735
43	 1,1-Di-(α-decalyl)octane	$C_{28}H_{50}$	6 (Glass)	0.9521	389.2 (50°)	10150	9665
44	 1,1-Di-(α-tetralyl)ethane	$C_{22}H_{26}$	24 (Glass)	1.0570	—	9675	9995

manner, according to [9], a transition from 1,1-dicyclohexylpentane to its 1,5-isomer causes the freezing point to decrease from 15.3 to -13.6°, and the volumetric heat of combustion to decrease from 9890 to 9380 kcal/liter, although their gravimetric heat capacity is the same (10,800 kcal/kg).

In the case of alkylcyclohexanes with approximately the same degree of branching the volumetric heat of combustion increased, as a rule, with increase in the molecular weight. A similar increase in the volumetric heat capacity was observed recently [19] in going from the isomeric nonylcyclohexanes (10,355 · 0.844 = 8740 kcal per liter) to the decyl- and then to the dodecylcyclohexanes (10,300 · 0.863 = 8890 kcal/liter). In contrast, in the 1,1-di-(α-decalyl)-alkane series with a normal aliphatic chain the freezing point, viscosity, density and volumetric heat capacity decreased uniformly with increase in the molecular weight from didecalylethane to didecalyloctane.

Among the isomeric alkylcyclohexanes and alkyldecalins obtained by us the density, volumetric heat capacity and viscosity increased in proportion to the number of tertiary, and especially the number of quaternary carbon atoms contained in the side chain. Thus, of the nonylcyclohexanes (formula $C_{15}H_{30}$) the lowest viscosity (4.0 centistokes at 20°) and volumetric heat of combustion (8545 kcal/liter) was possessed by the least branched 3-ethyl-1-cyclohexylheptane (No. 13, table), whereas for the most highly branched 1,2,2,4-tetramethyl-1-cyclohexylpentane (No. 15), ν^{20} = 5.3 centistokes and Q_b^n = 8745 kcal/liter. In like manner, also among the isomeric

α-octyldecalins (Nos. 35-38) both the viscosity and the volumetric heat of combustion increase with increase in the degree of branching of the side chain—from n-octyldecalin to 2,5-dimethyl-2-decalylhexane.

EXPERIMENTAL

The naphthene hydrocarbons listed in the table (with the exception of hydrocarbon No. 25) were obtained by the hydrogenation of the corresponding alkyl- and alkenylaromatic hydrocarbons in a rotated one-liter autoclave in the presence of 5-15 wt. % of Raney nickel. Either methylcyclohexane or ethanol served as the solvent in the hydrogenations.

Hydrogenation of the benzene rings to the cyclohexanes was accomplished at 160-180°, at an initial hydrogen pressure of 100-140 atm, and usually in a matter of 6-10 hr, while the naphthalene rings were reduced to the decalins at 180-200° and the same hydrogen pressure, in a matter of 8-10 hr for the alkyldecalins and 10-16 hr for the didecalylalkanes. Hydrogenation of the triphenylalkanes required 20-30 hr, in which connection the hydrogenizate usually contained both the tricyclohexylalkane and the corresponding dicyclohexylalkane, the latter formed due to cleavage of one of the rings.

Only 3,4-dimethyl-3,4-diphenylhexane could not be converted to the corresponding naphthene using Raney nickel; under the above indicated conditions (160-180°) it is converted completely to sec-butylcyclohexane, while at 120° it is not hydrogenated at all. Only when we replaced the Ni catalyst by Pt/C and dropped the hydrogenation temperature to 125° were we able to exclude the concurrent cracking of the skeleton of the molecule.

The catalytic hydrogenation of 1,1-di-(α-naphthyl)ethylene to 1,1-di-(α-tetralyl)ethane (only one of the four possible structures of this compound is given in the table under No. 44) was accomplished in methylcyclohexane medium, using 20 wt. % of copper-chromium catalyst, prepared according to [20], an initial hydrogen pressure of 135 atm, and a time of 8 hr.

Determination of the heat capacities was done by combustion in a calorimetric bomb, in accordance with GOST 5080-55. Conversion of the found total heat of combustion Q_b^t to the net Q_b^n was done using the formula $Q_b^n = Q_b^t - (\%\,H \cdot 54 + 12$ kcal), where % H is the percent content of hydrogen in the tested hydrocarbon. The freezing points of the hydrocarbons, congealing to a "glass," were determined in accordance with GOST 1533-42.

SUMMARY

1. Some new mono-, di-, tri- and tetracyclic naphthene hydrocarbons of variable structure were synthesized by us, and their freezing points, density, viscosity and heat capacities were determined.

2. It was shown that the density and volumetric heat capacity of hydrocarbons of approximately the same molecular weight increase (with a simultaneous decrease in the gravimetric heat capacity) in proportion to the number of naphthene rings in the molecule—from the alkanes to the 1,1-didecalylalkanes.

3. It was found that the freezing point, viscosity and volumetric heat of combustion of the 1,1-di-(α-decalyl)-alkanes decrease with increase in the molecular weight, whereas, in contrast, the freezing point and viscosity of the alkylcyclohexanes with the same degree of branching increase with increase in the molecular weight.

4. It was established that among the isomeric alkylcyclohexanes and α-alkyldecalins the density, volumetric heat capacity and viscosity increase in proportion to the number of tertiary, and especially the number of quaternary carbon atoms contained in the side chain.

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ISOXAZOLE COMPOUNDS

III. SYNTHESIS OF SOME ISOXAZOLYLAZOLES

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1781-1787, June, 1960
Original article submitted June 25, 1959

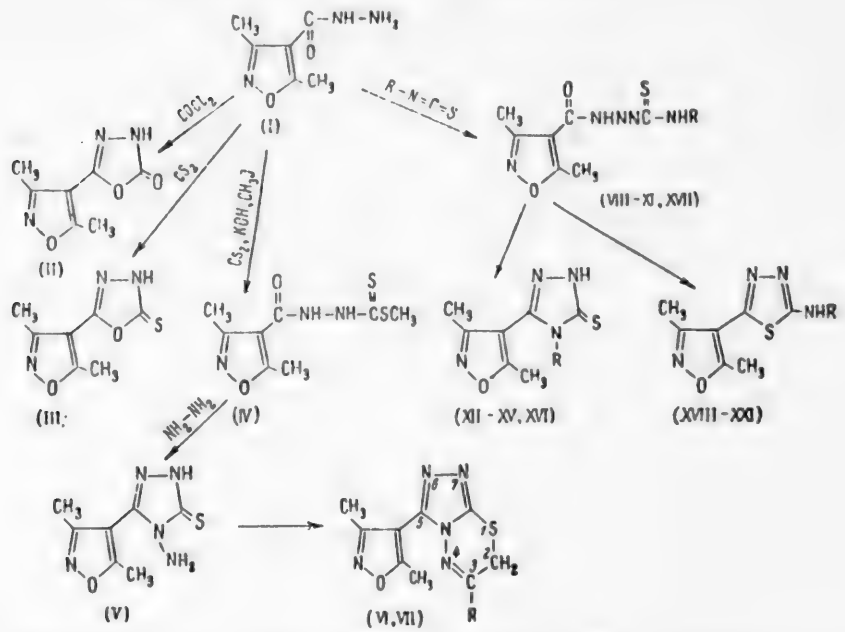
The purpose of the present study was to obtain some compounds in which the isoxazole ring is linked through a single bond with other azoles, like 1,3,4-thiadiazole, 1,3,4-oxadiazole and 1,3,4-triazole, containing functional groups (oxo-, thiono-, amino-). Compounds of this type with two heterocycles might possess interest for physiological testing.• The use of an isoxazole as one of the components in the indicated diazoles was based on the analogy in the action of certain isoxazole compounds with the action of pyridine derivatives [1], and also because of the discovery of the highly active isoxazole antibiotic—cycloserine [2].

We selected 3,5-dimethyl-4-isoxazoylhydrazide as the starting material for the synthesis of the biheterocycles. The hydrazide group makes it possible to attach other azole rings, while the 3,5-dimethylisoxazolyl radical is quite stable and has been used as a component part of a number of physiologically active compounds [1, 3]. Employing reactions known for hydrazides, we obtained a number of new biheterocyclic systems from 3,5-dimethyl-4-isoxazoylhydrazide (I). Thus, the passage of a stream of phosgene through a dioxane solution of hydrazide (I) gave us 5-(4'-isoxazolyl)-1,3,4-oxadiazole-2-one (II). A similar reaction for benzhydrazide and certain other hydrazides is described in the literature [4]. 5-Isoxazolyloxadiazole-2-thione (III) is obtained when isoxazoylhydrazide (I) is refluxed with carbon disulfide in alcohol. In alcoholic KOH solution the reaction of 3,5-dimethyl-4-isoxazoylhydrazide with carbon disulfide goes even in the cold with the formation of the potassium salt of dithiocarbazic acid. A water solution of this salt with methyl iodide gives the S-methyl ester of thiocarbazic acid (IV). 3-Isoxazolyl-4-aminotriazole-5-thione (V) is formed when this compound is refluxed with an alcohol solution of hydrazine hydrate. The preparation of similar aminotriazolethiones and oxadiazolethiones from the hydrazides of acids has already been described [5]. The structure of the isoxazolylamine obtained by us—triazolethione (V)—is confirmed by its ability to give the azomethine with benzaldehyde, and also by the infrared patterns. Aminotriazolethione (V) may be used to obtain the even more complicated triheterocyclic system. Thus, reaction of the compound with ω-bromoacetophenone or with chloroacetone yields the corresponding isoxazolyltriazolothiadiazines (VI, VII).

Isoxazoylhydrazide (I) adds smoothly to the p-chlorophenyl-, p-methoxyphenyl-, p-ethoxyphenyl, and α-naphthyl mustard oils with the formation of the corresponding 1-isoxazolyl-4-arylthiosemicarbazides (VIII-XI), which are colorless crystalline compounds that are difficultly soluble in the common solvents. The crude thiosemicarbazides can be converted to the readily crystallizing isoxazolyltriazolethiones (XII-XV) by refluxing

•Compounds in which two heterocycles are connected through the single bond, methylene bridge or ether oxygen are encountered quite frequently among highly active natural-occurring substances. Nicotine, anabasine, aneurine, pilocarpine, emetine, dicoumarol, and many other compounds have such a construction. A "doubling" of the heterocycles apparently plays an important role in imparting biological activity to these compounds.

Scheme for the Synthesis of Some Isoxazolylazoles



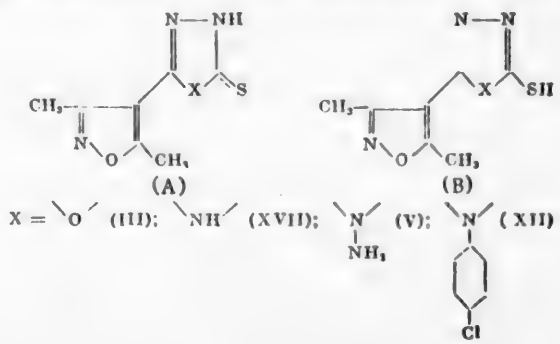
(VI) R = C_6H_5 ; (VII) R = CH_3 ; (VIII) R = p-C_6H_4Cl ; (IX) R = p-$C_6H_4OC_2H_5$; (X) R = p-$C_6H_4OCH_3$; (XI) R = α-$C_{10}H_7$; (XII) R = p-C_6H_4Cl ; (XIII) R = p-$C_6H_4OCH_3$; (XV) R = p-$C_6H_4OC_2H_5$; (XV) R = α-$C_{10}H_7$; (XVI) R = H; (XVII) R = H ; (XVIII) R = H ; (XIX) R = p-C_6H_4Cl ; (XX) R = p-$C_6H_4OCH_3$; (XXI) R = α-$C_{10}H_7$.

for a short time with dilute caustic solution. Similar compounds in the pyridine series were obtained by one of us earlier [6].

The unsubstituted isoxazolyltriazolethione (XVI) is obtained by refluxing 3,5-dimethylisoxazoylthiosemicarbazide (XVII) with sodium ethylate. The starting isoxazoylthiosemicarbazide (XVII) was obtained by acylating thiosemicarbazide with isoxazoyl chloride in pyridine.

Using acidic condensation agents, the isoxazoylthiosemicarbazide may be cyclized not only to triazoles, but also to the thiadiazoles. Treatment of isoxazoylthiosemicarbazide with concd. sulfuric acid at 100° yields 2-amino-5-isoxazolylthiadiazole (XVIII). Refluxing isoxazoylthiosemicarbazide with acetic anhydride gives the acetyl derivative of thiadiazole (XVIII). One of us had already prepared some biheterocyclic arylaminothiodiazoles earlier by the cyclization of 1-isonicotinoyl-4-arylthiosemicarbazides with either sulfuric acid or acetyl chloride [7]. In a similar manner 1-isoxazoyl-4-(p-chlorophenyl)-thiosemicarbazide cyclizes even in the cold to 2-(p-chlorophenyl)-amino-5-isoxazolylthiadiazole (XIX) when allowed to stand with concd. sulfuric acid for a short time. The methoxyphenylamino- and α-naphthylaminothiadiazoles (XX and XXI) are formed by the cyclization of the corresponding thiosemicarbazides with acetyl chloride.

Both the thione (A) and the thiol (B) structures are possible for compounds (III, V, XII, XVII).



(A) (B)

X = O (III); NH (XVII); N—NH$_2$ (V); N—C$_6$H$_4$Cl (XII)

A study of the infrared spectra of crystalline samples revealed that in all cases the spectra failed to show absorption bands in the 2600-2550 cm^{-1} region, characteristic for the SH group [8]. All of the studied compounds have absorption bands in the 3120-3110 cm^{-1} region, indicating the presence of the NH group. In addition, the investigated compounds show weak absorption in the 1520 cm^{-1} region, usually attributed to the >C = S grouping [9]. The spectrum of 3-isoxazolyl-4-aminotriazole-5-thione (V) shows four absorption bands at 3370, 3305, 3125, and 3060 cm^{-1}. Three of these four bands are characteristic for primary aromatic amines and one is characteristic for the NH group. As a result, the examined compounds have the structure of thiones (A) in the crystalline state.•

EXPERIMENTAL

3,5-Dimethyl-4-isoxazoylhydrazide was obtained in 92% yield. Lustrous needles with m.p. 129-130° (130-131°) [10].

Isoxazoylhydrazide (I) forms hydrazones in quantitative yield when heated for a short time with aldehydes in alcohol.

3,5-Dimethyl-4-isoxazoylbenzylidenehydrazone. The compound was obtained as colorless scales with m.p. 166-167° (from alcohol).

Found %: N 17.10. $C_{13}H_{13}O_2N$. Calculated %: N 17.28.

3,5-Dimethylisoxazoylfurfurylidenehydrazone was obtained as colorless tablets. M. P. 207-209°.

Found %: N 18.24. $C_{11}H_{11}O_3N_3$. Calculated %: N 18.02.

5-(3',5'-Dimethyl-4'-isoxazolyl)-1,3,4-oxadiazole-2-one (II). To 50 ml of dioxane saturated with phosgene was added a solution of 4 g of the isoxazoylhydrazide in 80 ml of dioxane, after which a stream of phosgene was passed into the mixture for 1.5 hr. The excess phosgene was blown out with carbon dioxide and the dioxane was evaporated under slight vacuum. Recrystallization from 10% alcohol gave 4.1 g (86%) of (II). Colorless prisms with m.p. 185-187°.

Found %: N 23.19. $C_7H_7O_3N_3$. Calculated %: N 23.20.

5-(3',5'-Dimethyl-4'-isoxazolyl)-1,3,4-oxadiazole-2-thione (III). A mixture of 1.5 g of hydrazide (I) and 2 ml of carbon disulfide was refluxed in 30 ml of alcohol until the evolution of hydrogen sulfide ceased (3-4 hr). At the end of reaction the alcohol was distilled and the residue was recrystallized from 10% alcohol. We obtained 1.4 g (70%) of colorless lustrous needles with m.p. 215-218° (decomp.).

Found %: N 21.46; S 16.35. $C_7H_7O_2N_3S$. Calculated %: N 21.30; S 16.26.

Methyl ester of 2-(3',5'-dimethyl-4'-isoxazoyl)-dithiocarbazic acid (IV). A mixture of 3.1 g of the isoxazoylhydrazide and 1.2 g of KOH was dissolved in 30 ml of anhydrous alcohol. Then 5 ml of carbon disulfide was added to the solution with vigorous stirring. A copious precipitate began to deposit, and soon the entire mass became solid. After several hours ether was added to the reaction mixture and the precipitate was filtered. The potassium salt was dissolved in water and the solution was treated with 4 ml of methyl iodide. The reaction mixture was stirred vigorously at room temperature, and here the methyl ester of the dithiocarbazic acid precipitated gradually. The next day the precipitate was filtered and washed with water until the odor of mercaptan was absent. Yield 4.4 g (90%). Colorless lustrous needles. M. p. 176-178° (from alcohol).

Found %: S 25.88. $C_8H_{11}O_2N_3S_2$. Calculated %: S 26.14.

3-(3',5'-Dimethyl-4'-isoxazolyl)-4-amino-1,2,4-triazole-5-thione (V). A mixture of 4.4 g of the methyl dithiocarbazate (IV) and 4 ml of 50% hydrazine hydrate was refluxed in 30 ml of alcohol for 6-8 hr. The alcohol was distilled off and the reaction mass was diluted with water, followed by acidification until acid to Congo. The obtained aminotriazolethione (V) was recrystallized from alcohol. Yield 2.5 g (66%). Fine colorless needles with m.p. 202-204°.

•Numerous observations by various authors [11] and our own data permit the general conclusion that cyclic monothioamides exist as thiones, and not as thiols, in the crystalline state.

Found %: N 33.16; S 15.29. $C_7H_9ON_5S$. Calculated %: N 33.16; S 15.18.

The benzylidene derivative was obtained as fine colorless needles with m.p. 230-232°.

Found %: N 23.32. $C_{14}H_{13}ON_5S$. Calculated %: N 23.40.

3-Phenyl-5-(3',5'-dimethyl-4'-isoxazolyl)-{[(1", 2", 4")-triazolo]-[3,4-b]-[(1"', 3"', 4"', 6"'-H)-thiadiazine]} (VI).* A mixture of 2 g of 3-(3,5-dimethyl-4-isoxazolyl)-4-amino-1,2,4-triazole-5-thione (V) and 2 g of ω-bromoacetophenone in 50 ml of anhydrous alcohol was refluxed for 2 hr. After removal of the alcohol the residue was washed first with dilute alkali, then with water, dilute acid, and again with water. Recrystallization from methyl alcohol gave 2.4 g (80%) of triazolothiadiazine (VI); flat colorless prisms; m.p. 187-189°.

Found %: N 22.18; S 10.19. $C_{15}H_{13}ON_5S$. Calculated %: N 22.50; S 10.30.

In a similar manner the reaction of aminotriazolethione (V) with chloroacetone gave 3-methyl-5-(3',5'-dimethyl-4'-isoxazolyl)-{[(1", 2", 4")-triazolo]-[3,4-c]-[1"', 3"', 4"', 6"'-H)-thiadiazine]} (VII) with m.p. 178-180° (from methyl alcohol). Yield 74%. Elongated colorless prisms.

Found %: S 12.98. $C_{10}H_{11}ON_5S$. Calculated %: S 12.86.

1-(3',5'-Dimethyl-4'-isoxazoyl)-4-(p-chlorophenyl)-thiosemicarbazide (VIII). Warm alcohol solutions of 1 g of the isoxazoyl hydrazide and 1.2 g of p-chlorophenyl mustard oil were poured together. After several minutes a precipitate of the isoxazoylthiosemicarbazide began to deposit. Yield 1.75 g (83%). The product is very difficultly soluble in the common solvents. It was recrystallized from a large volume of boiling chlorobenzene. Colorless scales with m.p. 165-167°.

Found %: N 17.34; S 9.90. $C_{13}H_{13}O_2N_4SCl$. Calculated %: N 17.25; S 9.87.

Reaction with other mustard oils was carried out in a similar manner. The following thiosemicarbazides were prepared: 1-(3',5'-dimethyl-4'-isoxazolyl)-4-(p-ethoxy)-phenylthiosemicarbazide (IX) (yield 75%, m.p. 216-218°); 1-(3',5'-dimethyl-4'-isoxazolyl)-4-(p-methoxy)-phenylthiosemicarbazide (X) (yield 80%, m.p. 206-208°); 1-(3',5'-dimethyl-4'-isoxazolyl)-4-(α-naphthyl)thiosemicarbazide (XI) (yield 40%, m.p. 166-167°).

The thiosemicarbazides are very difficultly soluble in the common solvents and were subjected to further transformations without special purification.

3-(3',5'-Dimethyl-4'-isoxazolyl)-4-(p-chlorophenyl)-1,2,4-triazole-5-thione (XII). 1-Isoxazoyl-4-(p-chlorophenyl)-thiosemicarbazide (VIII) (0.5 g) was refluxed for 15 min in 6 ml of 2N NaOH. The solution after cooling was acidified with hydrochloric acid to precipitate the triazolethione. The properties of the product are given in the table. The other triazolethiones (XIII-XV) were obtained in a similar manner.

1-(3',5'-Dimethyl-4'-isoxazolyl)-thiosemicarbazide (XVII). A suspension of 4.6 g of the thiosemicarbazide in 50 ml of dry pyridine was cooled to 0°, after which 8 g of vacuum-distilled 3,5-dimethyl-4-isoxazoyl chloride was added at a temperature ranging between 0 and 5°. The next day the pyridine was vacuum-distilled, and the isoxazoylthiosemicarbazide was recrystallized from 50% alcohol. The compound was obtained as colorless, elongated rectangular prisms with m.p. 220-222°. Yield 6.5 g (61%).

Found %: S 14.92. $C_7H_{10}O_2N_4S$. Calculated %: S 14.97.

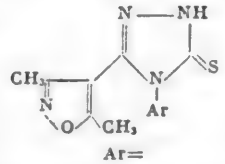
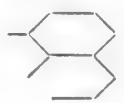
3-(3',5'-Dimethyl-4'-isoxazolyl)-1,2,4-triazole-5-thione (XVI). One gram of isoxazolylthiosemicarbazide (XVII) was refluxed for 12 hr with sodium ethylate (0.45 g of sodium in 12 ml of anhydrous alcohol). The solution was acidified with 0.5 N hydrochloric acid. The obtained triazolethione (XVI) was recrystallized from 50% alcohol. Yield 0.6 g (65%). Coarse colorless needles. M. p. 264-267° (decompn.).

Found %: N 28.30; S 16.62. $C_7H_8ON_4S$. Calculated %: N 28.55; S 16.34.

2-Amino-5-(3',5'-dimethyl-4'-isoxazolyl)-1,3,4-thiadiazole (XVIII). One gram of isoxazoylthiosemicarbazide (XVII) was dissolved in 5 ml of coned. sulfuric acid by heating on the boiling water bath, and the

*Hoggarth regards such compounds to be derivatives of 3,5-substituted 6,7-dihydro-7-thia-1 : 2 : 4 : 9-tetraazaindene [5].

Properties of Isoxazolylaryltriazolethiones

Compound No.	 Ar=	Empirical formula	Name	Yield (%)	Melting point*	% N		% S	
						found	calc.	found	calc.
(XII)		$C_{13}H_{11}ON_4SCl$	3-(3',5'-Dimethyl-4'-isoxazolyl)-4-(p-chlorophenyl)-1,2,4-triazole-5-thione	95	247—249°	18.04	18.26	10.21	10.45
(XIII)		$C_{14}H_{14}O_2N_4S$	3-(3',5'-Dimethyl-4'-isoxazolyl)-4-(p-methoxyphenyl)-1,2,4-triazole-5-thione	90	214—216	18.42	18.54	—	—
(XIV)		$C_{15}H_{16}O_2N_4S$	3-(3',5'-Dimethyl-4'-isoxazolyl)-4-(p-ethoxyphenyl)-1,2,4-triazole-5-thione	92	210—212	17.73	17.71	10.00	10.14
(XV)		$C_{17}H_{14}ON_4S$	3-(3',5'-Dimethyl-4' isoxazolyl)-4-(α-naphthyl)-1,2,4-triazole-5-thione	35	268	17.11	17.38	9.75	9.95

* All of the compounds were recrystallized from alcohol.

solution was allowed to stand overnight. The reaction mass was then poured over ice and alkalization with NaOH gave the free base as a precipitate. Yield 0.5 g (55%). Colorless prisms; m.p. 194-195° (from alcohol).

Found %: S 16.61. $C_7H_8ON_4S$. Calculated %: S 16.34.

Acetyl derivative, m.p. 236-237° (from alcohol).

Found %: N 23.45; S 13.36. $C_9H_{10}O_2N_4S$. Calculated %: N 23.51; S 13.45.

The same acetyl derivative is obtained in quantitative yield by heating the isoxazoylthiosemicarbazide (XVII) in acetic anhydride for 40 min under reflux.

2-(p-Chlorophenylamino)-5-(3',5'-dimethyl-4'-isoxazolyl)-1,3,4-thiadiazole (XIX). A solution of 1 g of 1-isoxazolyl-4-(p-chlorophenyl)-thiosemicarbazide (VIII) in 10 ml of concd. sulfuric acid was allowed to stand for 15 min and then it was poured into water. The free base was precipitated by the addition of concd. ammonia, and then it was recrystallized from alcohol. Yield 0.8 g (85%). Colorless needles with m.p. 230-232°.

Found %: S 10.37. $C_{13}H_{11}ON_4SCl$. Calculated %: S 10.45.

Acetyl derivative, m.p. 218-220° (with decompn.).

Found %: N 1593; S 9.13. $C_{15}H_{13}O_2N_4SCl$. Calculated %: N 16.06; S 9.19.

2-(p-Methoxyphenylamino)-5-(3',5'-dimethyl-4'-isoxazolyl)-1,3,4-thiadiazole (XX). Complete solution was obtained when a suspension of 1.5 g of 1-isoxazoyl-4-(p-methoxyphenyl)-thiosemicarbazide (X) in 15 ml of acetyl chloride was allowed to stand for 25-30 hr. At the end of this time the reaction mass was poured over ice and made alkaline with concd. ammonia. Recrystallization from alcohol gave 1 g (71%) of thiadiazole (XX). Colorless, flat rectangular prisms with m.p. 206-208°.

Found %: N 18.55; S 10.67. $C_{14}H_{14}O_2N_4S$. Calculated %: N 18.54; S 10.60.

2-(α-Naphthylamino)-5-(3',5'-dimethyl-4'-isoxazolyl)-1,3,4-thiadiazole (XXI) was obtained by stirring 1-isoxazoyl -4-(α-naphthyl)-thiosemicarbazide (XI) with acetyl chloride for 1 hr. Yield 65%. Colorless needles with m.p. 204-206°.

Found %: 17.10; S 9.75. $C_{17}H_{14}ON_4S$. Calculated %: N 17.38; S 9.95.

The infrared spectra were taken by L. F. Trefilova using an IKS-12 spectrograph. The spectra were taken in the 2.5-5μ region using a LiF prism, and in the 5-7 μ region using a NaCl prism. We will present the absorption band values for four of the compounds (III, V, XII, XVII) (in cm^{-1}).

(III): 3110 (s), 2940 (med), 2775 (med), 1640 (med), 1595 (med), 1520 (med).

(V): 3370 (s), 3305 (med), 3125 (s), 3060 (med), 2960 (med), 2775 (med), 1640 (med), 1590 (w), 1524 (med).

(XII): 3112 (s), 2945 (med), 2775 (med), 1650 (s), 1600 (med), 1520 (med).

(XVII): 3110 (s), 2945 (med), 2775 (med), 1650 (s), 1600 (med), 1520 (med).

SUMMARY

1. The following new isoxazole biheterocyclic compounds were obtained: isoxazolyloxadiazoles (II and III), isoxazolyltriazoles (V, VI, VII, XII-XVI), and isoxazolylthiadiazoles (XVIII-XXI).

2. By means of the infrared spectra it was shown that compounds (III, V, XII, XVII) have the thione, and not the thiol structure in the crystalline state.

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DERIVATIVES OF 10-UNDECYNOIC ACID

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1787-1791, June, 1960
Original article submitted June 9, 1959

Although investigators show considerable interest in the alkynecarboxylic acids, still the derivatives of these acids have remained relatively unstudied up to now. As we had reported earlier [1], one of the most readily available acids in this series, namely 10-undecynoic acid, possesses antiviral action. For this reason it seemed of interest to synthesize some derivatives of this acid and subject them to biological testing. Some of the compounds described below, for example, undecynoyl-p-phenethylthiourea and undecynoylbenzimidazole, were also synthesized because of papers reporting the existence of antiviral activity in a number of thiourea [2] and benzimidazole [3] derivatives.

10-Undecynoic acid is obtained from its isolog by the addition of bromine and subsequent cleavage of the elements of hydrobromic acid. The agents that have been used to dehydrobrominate 10,11-dibromoundecanoic acid include alcoholic KOH solution [4, 5], aqueous KOH solution [6], and sodium amide in liquid ammonia [7].

The method of obtaining the 10-undecynoic acid investigated was as in [8].

Because they were more convenient and safe, the dehydrobromination methods checked by us were those employing either alcoholic or aqueous KOH solution, and here the yields were 42 and 51.8%, respectively, based on 10,11-dibromoundecanoic acid. The latter is the most convenient of the mentioned methods, and it also possesses the additional advantage of giving reproducible results.

The reaction of 10-undecynoic acid with oxalyl chloride, and also with phosphorus pentachloride, gave 10-undecynoyl chloride in yields of 90 and 82%, respectively. Soon after this a paper appeared in the literature reporting the preparation of the same acid chloride by refluxing the acid with thionyl chloride [9] (yield 80%). This last method was also used by us, but without heating, and here the yield rose to 87%.

N-Undecynoylbenzimidazole was synthesized by reacting 10-undecynoyl chloride with a 100% excess of benzimidazole. The thiosemicarbazide of 10-undecynoic acid was obtained in a similar manner. Starting with 10-undecynoyl chloride, we also prepared the p-chlorophenyl ester, amide, and methylamide of 10-undecynoic acid, and also 10-undecynoyl isothiocyanate, which when reacted with p-phenetidine was converted to N-undecynoyl-N'-p-phenethylthiourea. The ureide of 10-undecynoic acid was obtained by reacting urea with the ethyl ester of the indicated acid in the presence of sodium ethylate and pyridine [10]. We also prepared the butyl ester and the copper salt of 10-undecynoic acid. The copper salt is a blue-green compound that is heat unstable. Thus, for example, the substance on melting changes from a green to a yellow color, while when refluxed in either ethyl acetate or alcohol the green solution gradually decolorizes, and a light-colored precipitate deposits. It was theorized by us that dimerization takes place here, which leads to the formation of eicosa-9,11-diyn-1,20-dicarboxylic acid [11]. Actually, when we refluxed a solution of the copper salt of 10-undecynoic acid in alcohol for 3 hr we isolated from the reaction products* an acid that was identical with the above dicarboxylic acid; the two

*An attempt to isolate other individual substances besides eicosa-9,11-diyn-1,20-dicarboxylic acid from the obtained mixture of acids proved unsuccessful.

acids had the same melting point, and the mixed melting point was not depressed. The counter synthesis of eicosa-9,11-diyn-1,20-dicarboxylic acid was effected by shaking 10-undecynoic acid in an oxygen atmosphere in the presence of ammoniacal cuprous chloride solution (75% yield).

The testing of the obtained compounds for bacteriostatic activity was done by S. N. Milovanova and A. L. Mikerina, while the antiviral testing was done by N. S. Bogdanova. Here it was established that the copper salt of 10-undecynoic acid in vitro neutralizes the virus group, while N-undecynoyl-N'-p-phenethylthiourea and the thiosemicarbazide of 10-undecynoic acid show activity against the human strain of tubercle bacillus.

EXPERIMENTAL

10-Undecynoic acid was synthesized by the method of [6], but here we improved on the method of working up the product. 10,11-Dibromoundecanoic acid (400 g) was added in portions to a solution of 526 g of KOH in 320 ml of water, the mixture stirred well, and then it was heated under reflux for 8 hr. The mixture after cooling was acidified with concd. hydrochloric acid until acid to Congo, and the obtained oily layer was vacuum-distilled, b.p. 165-200° at 16 mm. The distillate was cooled in ice, and here the crystalline material was carefully separated from oily impurities by filtration. Yield 113 g (51.8%), m.p. 38-41°.• After repeated recrystallization from petroleum ether (b.p. 60-80°), with the addition of small amounts of either alcohol or ether, the m.p. was 44.5°.

Found %: HC ≡ C— 13.74. $C_{11}H_{18}O_2$. Calculated %: HC ≡ C— 13.73.

Derivatives of 10-undecynoic acid. Acid chloride. a) A mixture of 10 g of 10-undecynoic acid and 25 g of oxalyl chloride (b.p. 62-63°) was heated under reflux for 30 min. After this the excess oxalyl chloride was distilled off and the residue was vacuum-distilled. Yield 90%.

b) An equivalent amount of 10-undecynoic acid was added in portions, with external cooling, to the phosphorus pentachloride, after which the mixture was allowed to stand at room temperature for 2 hr. Then the phosphorus oxychloride was vacuum-distilled, followed by distillation of the residue, also in vacuo. Yield 82%. Colorless mobile liquid with a characteristic odor. B. p. 135° at 15 mm, and 121° at 7 mm.

Found %: Cl 17.47. $C_{11}H_{17}OCl$. Calculated %: Cl 17.67.

Amide. 10-Undecynoyl chloride was added to an excess of 25% aqueous ammonia solution. The obtained precipitate was filtered, washed with water employing mechanical stirring, and then recrystallized from ethyl acetate. Yield 74%. Colorless crystalline compound, soluble in benzene and in alcohol. M.p. 99.5-101.5°.

Found %: N 7.58, 7.95. $C_{11}H_{19}ON$. Calculated %: N 7.72.

Methylamide. A solution of 11.5 g of 10-undecynoyl chloride in 22 ml of benzene was added gradually, with stirring, at a temperature not exceeding 0°, to 20 ml of 25% aqueous methylamine solution. At the end of addition the mixture was stirred at the same temperature for another 15 min, after which the precipitate was filtered and washed with 30 ml of water, employing mechanical stirring. Yield 90%. Colorless crystalline compound, readily soluble in the common organic solvents. The compound was recrystallized from petroleum ether. M.p. 40-41°.

Found %: N 7.30, 7.11. $C_{12}H_{21}ON$. Calculated %: N 7.18.

N-Undecynoylbenzimidazole. A solution of 10-undecynoyl chloride in benzene was shaken with a 100% excess of benzimidazole for 12 hr, after which the benzimidazole hydrochloride was filtered and the benzene was distilled from the filtrate in vacuo. Yield 88%. Colorless crystalline compound, soluble in the common organic solvents. It was recrystallized from petroleum ether containing a little ethyl alcohol. M.p. 65-66°. Not stable to storage.

Found %: N 10.04, 10.10. $C_{18}H_{22}ON_2$. Calculated %: N 9.92.

Thiosemicarbazide. A mixture of 2 g of 10-undecynoyl chloride and 1.8 g of thiosemicarbazide was stirred for 6 hr, after which the mixture was allowed to stand for 36 hr, then washed with water employing mechanical

•From the literature [4, 7]: m.p. 42-43.5°. However, determination of the amount of ethynyl group present revealed that the indicated acid with m.p. 43.5°, obtained after several recrystallizations from petroleum ether, is not entirely pure.

stirring, and finally the compound was extracted with hot methyl alcohol; the residue from the evaporation of the methyl alcohol was recrystallized from a mixture of benzene with a small amount of alcohol. Colorless crystalline compound, soluble in hot ethyl acetate. M.p. 125-126°.

Found %: S 12.66; N 16.52. $C_{12}H_{21}ON_3S$. Calculated %: S 12.56, N 16.45.

N-Undecynoyl-N'-p-phenethylthiourea. Three grams of 10-undecynoyl chloride was added gradually, with stirring, to a suspension of 3.2 g of lead thiocyanate in 3 ml of boiling benzene. At the end of addition the stirring was continued for another hour at benzene reflux. Then the precipitate was filtered, the benzene was distilled from the filtrate, and the residue was vacuum-distilled. The product was 10-undecynoyl isothiocyanate, which was obtained as a colorless liquid with a slight odor. B.p. 179° at 17 mm. Yield 2.4 g (70%).

A solution of the obtained 10-undecynoyl isothiocyanate in 5 ml of benzene was added gradually, with stirring, to a solution of 1.5 g of p-phenetidine in 5 ml of boiling benzene. At the end of addition the mixture was stirred for another hour at benzene reflux. The precipitate obtained on cooling was recrystallized from alcohol. Yield 3 g (77%). Colorless crystalline compound, soluble in the common organic solvents. M.p. 69-70°.

Found %: S 9.08, N 7.64. $C_{20}H_{28}O_2N_2S$. Calculated %: S 8.89, N 7.77.

p-Chlorophenyl ester. A mixture of equivalent amounts of 10-undecynoyl chloride and p-chlorophenol was allowed to stand in a vacuum-desiccator over solid KOH for 3 days. Here the p-chlorophenol gradually went into solution and hydrogen chloride was evolved. Then the reaction mixture was dissolved in ether, the solution washed with 2 N NaOH solution, then with water, and after the usual treatment the product was vacuum-distilled. Yield 77%. B.p. 163° at 1 mm. The distillate crystallized on standing. Colorless crystalline compound, soluble in alcohol, ether, and acetone. M.p. 28-29°.

Found %: Cl 12.10, 12.08. $C_{17}H_{21}O_2Cl$. Calculated %: Cl 12.11.

Ureide. A solution of 2 g of sodium metal in 22 ml of anhydrous alcohol was treated with 7 ml of pyridine and 1.2 g of finely powdered urea, and the mixture was heated until complete solution was obtained. After cooling, 2.7 g of ethyl 10-undecynoate was added and the mixture was allowed to stand for 3 days, after which it was poured into 30 ml of dilute acetic acid (1 : 1). The obtained precipitate was filtered, followed by washing with acetic acid (1 : 1), water, and alcohol. Yield 60%. Colorless crystalline substance, soluble in ethyl acetate and chloroform. After recrystallization from alcohol, m.p. 168°.

Found %: N 12.47, 12.68. $C_{12}H_{20}O_2N_2$. Calculated %: N 12.49.

p-Bromophenacyl ester. 10-Undecynoic acid was neutralized with an alcohol solution of NaOH, and then it was refluxed with an equivalent amount of p-bromophenacyl bromide in alcohol solution for 2 hr. After this the solution was cooled to + 5° and the crystalline product was filtered. Yield 75%. Colorless crystalline compound, readily soluble in benzene, acetone, dichloroethane, ethyl acetate, and ether; after recrystallization from alcohol, m.p. 71.5°.

Found %: Br 21.00, 21.22. $C_{19}H_{23}O_3Br$. Calculated %: Br 21.07.

Butyl ester. 10-Undecynoic acid was refluxed with double its weight of 2% hydrogen chloride solution in butyl alcohol for 6 hr. After the usual treatment, the product was vacuum-distilled. Yield 70%. Colorless mobile liquid with a slight odor. B.p. 170° at 16 mm.

Found %: C 75.33, H 11.16. $C_{15}H_{26}O_2$. Calculated %: C 75.57, H 10.99.

Copper salt. A solution of 7.15 g of crystalline sodium carbonate in 30 ml of water was heated with 9.1 g of 10-undecynoic acid to 50°. The obtained solution was treated with a solution of 6.25 g of copper sulfate hydrate in 30 ml of water. The obtained precipitate was filtered, washed with water, and dried in a vacuum-desiccator. The yield was quantitative. The salt was a blue-green powder, soluble in hot benzene; it was recrystallized from ethyl acetate. The melting point when the temperature was raised at a rate of 3° per minute was 119-120°.

Found %: Cu 14.91. $C_{22}H_{34}O_4Cu$. Calculated %: Cu 14.91.

Eicosa-9,11-diyn-1,20-dicarboxylic acid.* A solution of 9.9 g of cuprous chloride and 30 g of ammonium chloride in 150 ml of 0.08 N hydrochloric acid was added to a solution of 18.2 g of 10-undecynoic acid in 150 ml of alcohol. The obtained solution was shaken in an oxygen atmosphere until the absorption of oxygen ceased. Then the solution was acidified with 170 ml of 2 N hydrochloric acid and the obtained precipitate was filtered, washed with water, and recrystallized from alcohol. Yield 13.6 g (75%). M.p. 112-113.5°.

SUMMARY

A number of 10-undecynoic acid derivatives were synthesized: some amides and esters, the ureide, thiosemicarbazide, N-undecynoyl-N'-p-phenethylthiourea, etc.

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*The formation of this acid as a byproduct in the oxidative condensation of 1-hexyne with 10-undecynoic acid is described in the literature [11].

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REACTIVITY OF THE METHYL GROUP IN DERIVATIVES OF SYMMETRICAL METHYLTRIAZINE

II. COUPLING WITH DIAZO COMPOUNDS

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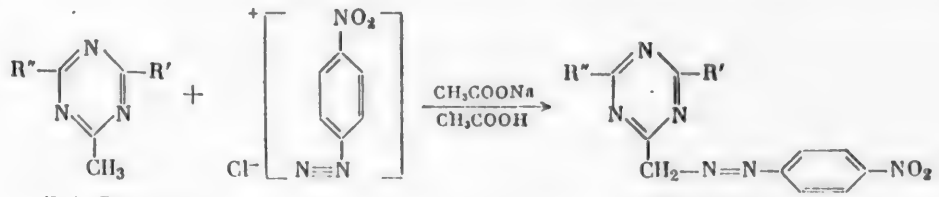
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1791-1798, June, 1960
Original article submitted May 7, 1959

It was shown by us in the previous paper [1] that derivatives of S-methyltriazine condense at the methyl group with various aldehydes, giving the corresponding styryl derivatives. The activating influence exerted by the triazine ring on the methyl group is so great here that all of the methyltriazines investigated by us enter into condensation with aldehydes. For this reason it is impossible to use the condensation reaction with aldehydes as a criterion of the deactivating influence exerted by electron-donor substituents (NH_2, OH, OCH_3), found in the 2 and 6 positions of the heterocyclic ring. It might be expected that this difference could be shown by studying the ability of the investigated triazines to enter into the azo-coupling reaction, since only a very few, highly reactive compounds have methyl groups in which the hydrogens are sufficiently active to enter into this reaction [2].

There is no information in the literature on whether methyltriazine derivatives are capable of entering into the azo-coupling reaction. We used p-nitrodiazobenzene as the diazo component; glacial acetic acid and 5% aqueous hydrochloric acid were used as the reaction medium. As the experiments revealed, nearly all of the methyltriazine derivatives investigated by us enter into the azo-coupling reaction.

Azo-coupling in glacial acetic acid medium. Dihydromethyltriazine (IA), aminohydroxymethyltriazine (IB) and dimethoxymethyltriazine (ID) react with p-nitrodiazobenzene in accordance with the following scheme:



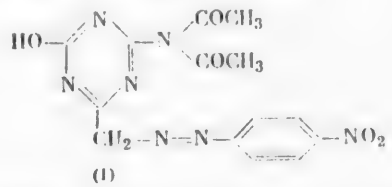
(I A, B, C, D) (II A, B, D)

A: $R' = R'' = OH$, C: $R' = R'' = NH_2$,
B: $R' = NH_2$, $R'' = OH$, D: $R' = R'' = OCH_3$.

Diaminomethyltriazine (IC) does not enter into the indicated reaction. The dihydroxymethyltriazine gives the highest yield of the azo product (about 60%). The aminohydroxymethyltriazine and dimethoxymethyltriazine give the azo products in lower yield (about 30%). The obtained azo products are very difficultly soluble in the common organic solvents and for this reason their purification is difficult. Despite the very low solubility of the azo products in alcohol, their alcohol solutions assume an intense color from the addition of either one or several drops of 0.1 N NaOH solution. The appearance of a color (blue, green) serves as a qualitative test for detecting the azo-coupling products.

The coupling of the aminohydroxymethyltriazine (IB) with p-nitrodiazobenzene gives an azo product that we were unable to obtain analytically pure. For this reason we decided to characterize it as the acetyl derivative. The diacetyl derivative is formed when azo product (IIB) is refluxed in a mixture of acetic anhydride and glacial acetic acid (4 : 1), which is obtained analytically pure by recrystallization from a mixture (4 : 1) of the above indicated solvents.

It is conceivable for methyltriazine derivatives containing OH and NH_2 groups to exist in different tautomeric forms [3]. For this reason it is impossible to consider the position of both of the acetyl groups in the diacetyl derivative of our azo compound as being established. However, structure (I) seems to be the most probable to us, i.e., the molecule contains the diacetylamino group.



(I)

It does not seem very probable that the acetyl radical is attached to the hydroxyl, since hydroxy derivatives of triazine, as well as of pyrimidine, cannot be acetylated.

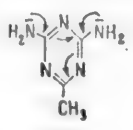
Finally, it should be mentioned that in the pyridine series 3-aminopyridine also forms the diacetyl derivative with ease, the same as does 2-aminopyridine, although in the case of 3-aminopyridine the possibility of the tautomeric transition of hydrogen from the NH_2 group into the ring is absent, and consequently it is conceivable for its diacetyl derivative to have only one structural formula, namely that containing the diacetylamino group.

The preparation of the azo compound from dimethoxymethyltriazine and p-nitrodiazobenzene seems important to us for the reason that the dimethoxymethyltriazine does not have any labile hydrogen atoms, other than those contained in the methyl group. For this reason there can be no doubt but that the azo product obtained from it is the p-nitrobenzeneazomethyl derivative.

A small amount of a brownish substance with m.p. 218-221° (decomp.) is isolated from the reaction solution when it is attempted to azo-couple the diaminomethyltriazine with p-nitrodiazobenzene. However, based on the elemental composition, this brownish substance is not the azo-coupling product of the starting reagents.• In addition, the obtained substance does not give the characteristic color reaction with caustic. In order to determine if this substance is the decomposition product of azo compound (IIC), we ran a special experiment. A reaction mixture was prepared, having a composition similar to that described below (see EXPERIMENTAL), but instead of the diaminomethyltriazine we took guanidine (having a basicity close to that of the diaminomethyltriazine) for the reaction. Here we obtained a brownish substance that was identical with that obtained earlier: the mixed melting point was not depressed. The elemental composition of the obtained product was close to that of p,p'-dinitroazobenzene, but the mixed melting point with authentic p,p'-dinitroazobenzene was depressed. We did not make a more detailed study of the obtained product.

Consequently, in the diaminomethyltriazine the methyl group is insufficiently active to enter into the azo-coupling reaction.

Amino groups, found in the 2 and 6 positions (IC), having a greater electron-donor capacity than hy-



(IC)

droxyl groups, cause a substantial reduction in the positive charge (δ^+) on the carbon atom attached to the methyl group. As a result of this, the mobility of the hydrogen atoms in the

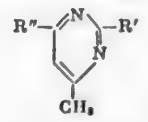
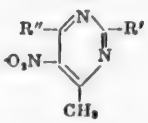
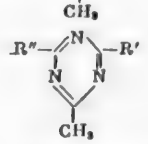
•Found %: C 54.36, 54.09, H 2.99, 2.74; N 20.23, 20.03. The azo-coupling product (IIC) should have, in %: C 43.80; H 3.68; N 40.88.

TABLE 1

Condensation conditions	Color	Melting point	Structure
In glacial acetic acid	Reddish-brown	309-312°(decompn.)	Azo structure (IIA)
In 5% hydrochloric acid	Yellow	338 (decompn.)	Hydrazone (IIa)

TABLE 2

Coupling of the Derivatives of 4-Methylpyrimidine, 5-Nitro-4-methylpyrimidine and the Corresponding Derivatives of 4-Methyltriazine with p-Nitrodiazobenzene in Glacial Acetic Acid Medium

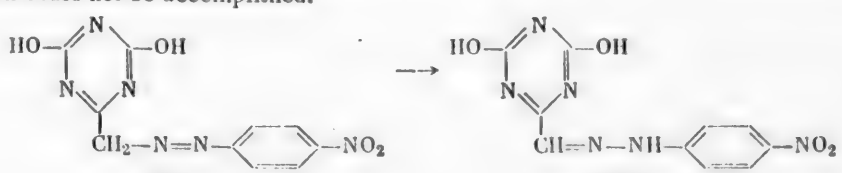
	$R'=R''=OH$	$R'=NH_2$, $R''=OH$	$R'=R''=NH_2$	$R'=R''=NHCOCH_3$	$R'=R''=OCH_3$
	Does not couple [7]	Does not couple [7]	Does not couple [7]	No data	No data
	Couples [8]	Does not couple*[8]	Couples [8]	No data	No data
	Couples	Couples	Does not couple	Couples	Does not couple

*2-Hydroxy-6-amino-4-methyl-5-nitropyrimidine couples with p-nitrodiazobenzene [8].

methyl group proves to be insufficient for reaction with p-nitrodiazobenzene. We attempted to reduce the deactivating influence of the amino groups in the diaminomethyltriazine by introducing acetyl radicals. By refluxing guanidine carbonate in acetic anhydride [4] we obtained 2,6-diacetyldiamino-4-methyltriazine and then coupled it with p-nitrodiazobenzene in glacial acetic acid medium. Here a reddish-brown product was formed, the alcohol solution of which turns dark green when one or several drops of 0.1 N NaOH solution is added. This characteristic property of the obtained substance leads us to assume that the azo product is formed when the diacetyldiaminomethyltriazine is reacted with p-nitrodiazobenzene.

Azo-coupling in 5% aqueous hydrochloric acid. Besides an acetic acid medium, we decided to run the azo-coupling reaction in 5% aqueous hydrochloric acid, since this medium had proved to be the most suitable for running the condensation of the corresponding methyltriazines with aldehydes [1]. In 5% hydrochloric acid medium the dihydroxymethyltriazine (IA) forms with p-nitrodiazobenzene a condensation product that is isomeric with (IA). The properties of the isomers are given in Table 1.

Isomer (IIA) is converted to isomer (IIa) when it is refluxed for a long time (8 hr) in nitrobenzene. The reverse transition could not be accomplished.



(II A) (II a)

Isomer (IIA), being more deeply colored, apparently has the azo structure, while isomer (IIa) has the hydrazone structure. A similar irreversible transformation of the red azo compound to the yellow hydrazone was described for the condensation products of 2,4,6-trinitrotoluene with p-nitrodiazobenzene [5]. In 5% hydrochloric acid medium the aminohydroxymethyltriazine (IB) forms with p-nitrodiazobenzene the p-nitrophenylhydrazone of 2,6-dihydroxy-4-formyltriazine (IIa). As a result, together with condensation, in the given case the amino group is replaced by hydroxyl under the influence of mineral acid. Similar cases where amino derivatives of the triazine series are hydrolyzed by mineral acid have been described in the literature [6].

The behavior of the diamino-, diacetyldiamino- and dimethoxymethyltriazines is similar to that of the aminohydroxymethyltriazine. In 5% hydrochloric acid they all form the same product with p-nitrodiazobenzene, namely, the p-nitrophenylhydrazone of 2,6-dihydroxy-4-formyltriazine (IIa). Consequently, in all of these cases, together with condensation, the above indicated groups (NH_2, $NHCOCH_3$, OCH_3) are hydrolyzed to hydroxyl under the influence of dilute hydrochloric acid.

As a result, a study of the reaction of p-nitrodiazobenzene with various methyltriazines revealed that in these compounds the methyl group is least active when two amino groups are present in the molecule. Replacing one or both amino groups by either hydroxyl or methoxyl, or by the acetamido group, raises the activity of the methyl group: the compound acquires the ability to azo-couple with p-nitrodiazobenzene.

A comparison of the activities of the methyl derivatives of triazine and of the corresponding derivatives of pyrimidine and 5-nitropyrimidine is given in Table 2. As can be seen from the data in Table 2, the triazine ring exerts a greater activating influence on the methyl group than does the pyrimidine nucleus. All of the methyltriazines investigated by us, with the exception of the diaminomethyltriazine, couple with p-nitrodiazobenzene. (In their activity the triazine derivatives approach the corresponding pyrimidine derivatives where a nitro group is present in the 5 position of the heterocycle).

EXPERIMENTAL

Coupling of dihydroxymethyltriazine with p-nitrodiazobenzene in glacial acetic acid medium. A mixture of 0.82 g (0.005 mole) of the dihydroxymethyltriazine hydrochloride and 3.4 g of sodium acetate was dissolved with heating in 30 ml of glacial acetic acid, after which the solution was cooled to room temperature. A solution of 0.7 g (0.005 mole) of p-nitroaniline in 2 ml of concd. hydrochloric acid and 1.5 ml of water was prepared by heating; the obtained solution was cooled rapidly (with stirring). Then a solution of 0.4 g of sodium nitrite in 2 ml of water was added to the p-nitroaniline hydrochloride, and here a yellowish-green solution was obtained. When the two solutions were poured together the resulting reaction mixture gradually changed from a yellow color to a reddish-brown. After 2 hr a voluminous reddish-brown precipitate deposited. The precipitate was allowed to stand overnight, after which it was filtered and washed several times with warm water. Yield 0.7 g (56%). M.p. around 300° (decompn.). The product is difficultly soluble in the common organic solvents. It was purified by refluxing first in acetic acid and then in alcohol. M. p. 309-312° (decompn.). The product gives characteristic changes in the color of the solution at different pH values (Table 3).

Found %: C 43.30, 43.36; H 2.98, 2.93; N 30.19, 30.14. $C_{10}H_8O_4N_6$. Calculated %: C 43.48; H 2.92; N 30.43.

TABLE 3

pH	Color of solution
10	Light green
11	Blue with a greenish tinge
12	Blue with a violet tinge
13	Violet

The product remains unchanged when refluxed in a mixture of acetic anhydride and glacial acetic acid (4 : 1). The reddish-brown azo product converts to the yellow-orange hydrazone (see below) when refluxed for 8 hr in nitrobenzene.

Coupling of aminohydroxymethyltriazine with p-nitrodiazobenzene in glacial acetic acid medium. A mixture of 5 g (0.04 mole) of the aminohydroxymethyltriazine and 11 g of anhydrous sodium acetate was dissolved with heating in 150 ml of glacial acetic acid, after which the solution was cooled to room temperature. Then the diazo solution, prepared from 5.5 g of p-nitroaniline (0.04 mole), 15 ml of concd. HCl, 10 ml of water and 3 g of sodium nitrite dissolved in 15 ml of water, was added. On standing overnight the solution acquired a dark brown color, and a dark brown precipitate deposited from the solution. Yield 1.4 g (13%). Dilution of the acetic acid filtrate gave an

TABLE 4

Starting product (in moles)	Amt. of 5% HCl (in ml)	Diazo solution	Yield
Aminohydroxymethyltriazine (0.005)	20	0.7 g of p-nitroaniline, 2 ml of concd. HCl, 1.5 ml of water, 0.4 g of $NaNO_2$ in 2 ml of H_2O	0.14 g (10%)
Diaminomethyltriazine (0.005)	20	0.7 g of p-nitroaniline, 2 ml of concd. HCl, 1.5 ml of H_2O, 0.4 g of $NaNO_2$ in 2 ml of H_2O	0.11 g (8%)
Diacetyldiaminomethyl-triazine (0.01)	25	1.38 g of p-nitroaniline, 3.8 ml of concd. HCl, 2.5 ml of H_2O, 0.75 g of $NaNO_2$ in 3.8 ml of H_2O	0.93 g (26%)
Dimethoxymethyltriazine (0.002)	10	2.8 g of p-nitroaniline, 8 ml of concd. HCl, 6 ml of H_2O, 1.4 g of $NaNO_2$ in 6 ml of H_2O. For reaction the obtained diazo solution is taken in 0.1 aliquots.	0.33 g (56%)

additional 3.2 g of precipitate. Total yield of azo product 4.6 g (42.5%). The compound is difficultly soluble in the common organic solvents. It was purified by refluxing in turn in water, alcohol, and glacial acetic acid. M.p. around 300° (decompn.). An alcohol solution of the product assumes a dark green color when 0.1 N NaOH solution is added.

Found %: N 36.38, 36.54. $C_{10}H_9O_3N_7$. Calculated %: N 35.64.

Recrystallization of the substance from a mixture of acetic anhydride and glacial acetic acid (4 : 1) gave a product that had m.p. 246-247° (decompn.). An alcohol solution of the recrystallized material assumes a blue-green color when 0.1 N NaOH solution is added. The obtained substance is the diacetyl derivative of 2-amino-6-hydroxy-4-(p-nitrobenzeneazomethyl)triazine.

Found %: C 46.62; 46.66; H 3.34, 3.31; N 27.37, 27.06. $C_{14}H_{13}O_5N_7$. Calculated %: C 46.77; H 3.64; N 27.29.

Coupling of diacetyldiaminomethyltriazine with p-nitrodiazobenzene in glacial acetic acid medium. Sodium acetate (11.4 g) was dissolved with heating in 60 ml of glacial acetic acid, the solution cooled to room temperature, and then 2 g (0.01 mole) of the diacetyldiaminomethyltriazine was added. The obtained clear, pale yellow solution was then treated with the diazo solution, prepared from 1.38 g (0.01 mole) of p-nitroaniline, 3.8 ml of concd. HCl, 2.5 ml of water, and a solution of 0.72 g of sodium nitrite in 4 ml of water. A reddish-brown precipitate deposited from the reaction solution on standing overnight. The substance is difficultly soluble in the common organic solvents. It was purified by refluxing in turn in water, nitrobenzene, dioxane, and alcohol. M.p. 278-279° (decompn.). The substance was colored reddish-brown. An alcohol solution of the substance assumes a dark green color when one or several drops of 0.1 N NaOH solution is added.

Coupling of dimethoxymethyltriazine with p-nitrodiazobenzene in glacial acetic acid medium. A mixture of 0.3 g (0.002 mole) of the dimethoxymethyltriazine and 1.6 g of sodium acetate was dissolved with heating in 10 ml of glacial acetic acid, after which the solution was cooled to room temperature. Then the diazo solution, prepared from 0.28 g (0.002 mole) of p-nitroaniline, 1 ml of concd. HCl, 1 ml of water, and a solution of 0.15 g of sodium nitrite in 1 ml of water, was added. On standing overnight the solution turned brown, but the azo product failed to precipitate. The substance was isolated by adding water. Yield 0.14 g (24%). M.p. 195-198° (decompn.). The substance is difficultly soluble in the common organic solvents. It was purified by refluxing in methyl alcohol. M.p. 215-216° (decompn.). A solution of the substance in alcohol assumes a blue color when one or several drops of 0.1 N NaOH solution is added.

Found %: C 46.70, 46.73; H 3.45, 3.17; N 28.10, 27.60. $C_{12}H_{12}O_4N_6$. Calculated %: C 47.35; H 3.98; N 27.60.

Coupling of dihydroxymethyltriazine with p-nitrodiazobenzene in dilute hydrochloric acid medium. A solution of 0.82 g (0.005 mole) of the dihydroxymethyltriazine hydrochloride in 20 ml of 5% hydrochloric acid was prepared by heating, after which it was cooled to room temperature. Then the diazo solution, prepared from 0.7 g (0.005 mole) of p-nitroaniline, 2 ml of concd. HCl, 1.5 ml of water and 0.4 g of sodium nitrite dissolved in 2 ml of water, was added. A precipitate deposited from the yellow solution on standing overnight. Yield 0.54 g. Another 0.27 g of substance deposited from the filtrate on standing. Total yield 59%. The product is difficultly soluble in alcohol, dioxane, pyridine, acetone and acetic acid, and is insoluble in benzene, toluene and carbon tetrachloride. It was purified by treating it several times with boiling glacial acetic acid. M.p. around 338° (decompn.). The color was yellow. This substance (hydrazone, IIa) when refluxed in nitrobenzene for 8 hr does not change to the azo product (IIA). An alcohol solution of the substance assumes a reddish-violet color when one or several drops of 0.1 N NaOH solution is added.

Found %: C 43.51, 43.18; H 3.08, 3.12; N 30.15, 30.13. $C_{10}H_8O_4N_6$. Calculated %: C 43.48; H 2.92; N 30.43.

The coupling of the aminohydroxy-, diamino-, diacetyldiamino - and dimethoxymethyltriazines with p-nitrodiazobenzene in dilute hydrochloric acid is given in Table 4.

In all four cases the same product is obtained from the azo-coupling reaction. From the properties and elemental analysis this product is the p-nitrophenylhydrazone of 2,6-dihydroxy-4-formyltriazine (IIa).

Found %: C 43.34, 43.26; H 3.11, 3.27; N 30.01, 30.14. $C_{10}H_8O_4N_6$. Calculated %: C 43.48; H 2.92; N 30.43.

SUMMARY

1. A study was made of the reaction of p-nitrodiazobenzene with the dihydroxy-, aminohydroxy-, diamino-, diacetyldiamino- and dimethoxymethyltriazines in either glacial acetic acid or dilute hydrochloric acid medium. All of the enumerated methyltriazines, except the diaminomethyltriazine, enter into the azo-coupling reaction in glacial acetic acid medium.

2. The coupling product of the dihydroxymethyltriazine with p-nitrodiazobenzene was obtained as two isomers. The brown isomer (azo product) changes to the yellow isomer (hydrazone) when refluxed in nitrobenzene.

When triazine derivatives containing the amino-, acetylamino-, or methoxyl group are reacted with p-nitrodiazobenzene in dilute hydrochloric acid medium, the azo- coupling reaction is accompanied by the simultaneous hydrolysis of these groups to the hydroxyl group.

3. The triazine ring greatly enhances the reactivity of a methyl group attached to it. This activating influence is greater in the case of the triazine ring than in the case of the pyrimidine ring, and this difference is even greater when compared to the pyridine ring. In its activating influence the triazine ring approaches that of 5-nitropyrimidine.

4. The diaminomethyltriazine is incapable of entering into the azo-coupling reaction. The amino groups, when compared to the hydroxyl or methoxyl groups, exert a greater deactivating influence on the methyl group.

5. Introduction of acetyl radicals into the amino group reduces the deactivating influence of the latter; the diacetyldiaminomethyltriazines are capable of entering into the azo-coupling reaction.

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ALKYLATED AROMATIC AMINES

I. METHYLATED DERIVATIVES OF PHENYLENEDIAMINES

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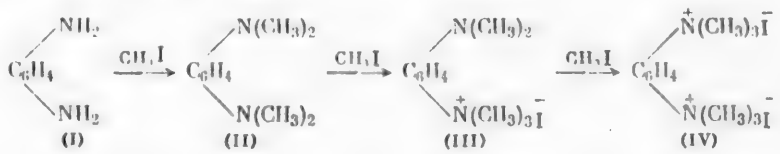
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1798-1805,
June, 1960
Original article submitted May 13, 1959

In this paper we studied the reaction of methyl iodide with the phenylenediamines (o-, m-, and p-) for the purpose of obtaining their methylated derivatives. The methylation of the amino groups occurring here can be depicted by the following scheme:



To synthesize the phenylene-bis-trimethylammonium salts (IV) we used the earlier described method for obtaining quaternary ammonium salts of the aromatic series [1]. In accordance with this method a solution of the phenylenediamine (I) in dilute methyl alcohol was refluxed with excess methyl iodide in the presence of calcium carbonate for 10 hr. Under these conditions both the m- and the p-phenylenediamine were converted in good yields (89.3, 68.1%) to the corresponding bis-quaternary ammonium bases, while the o-phenylenediamine under the same conditions was converted only to the hydriodide of tetramethyl-o-phenylenediamine. The obtained hydriodide of the ditertiary base has the composition $C_6H_4[N(CH_3)_2]_2 \cdot HI$, and m.p. 198-199°. In aqueous solution it can be titrated with alkali in the presence of phenolphthalein, differing from the mono- and bis-quaternary salts (III and IV) in this respect.

The tetramethyl-o-phenylenediamine, isolated from this salt by treatment with alkali, is converted to the mono-quaternary salt—trimethyl-o-dimethylaminophenylammonium iodide—when heated for several hours in aqueous methyl alcohol with excess methyl iodide. The bis-quaternary salt is not formed here, which is in agreement with the data existing in the literature [2]. Apparently, this is explained by steric hindrance, and also by the negative induction effect of the quaternary ammonium group, found ortho to the $N(CH_3)_2$ group.

We also reacted o-phenylenediamine with ethyl iodide in the presence of calcium carbonate. Also in this case the reaction stopped at the stage of obtaining the hydriodide of tetraethyl-o-phenylenediamine. The obtained salt has the composition $C_6H_4[N(C_2H_5)_2]_2 \cdot HI$, and can be titrated in aqueous solution with alkali in the presence of phenolphthalein.

This method of obtaining the ditertiary and tertiary-quaternary derivatives is not suitable for the case of the m- and p-isomers, since under these conditions, as was indicated above, the bis-quaternary salts of the alkylated m- and p-phenylenediamines are formed. It proved that these salts can be converted to the tertiary-quaternary derivatives by refluxing with aqueous KOH solution (7%). Refluxing m-phenylene-bis-trimethylammonium iodide with an alcohol solution of sodium ethylate leads to the formation of the ditertiary base.

Name of base	K_b*
o-Phenylenediamine [3]	$10^{-9.7}$
Tetramethyl-o-phenylenediamine	$10^{-7.8}$
Tetraethyl-o-phenylenediamine	$10^{-6.7}$
m-Phenylenediamine [3]	$10^{-9.4}$
Tetramethyl-m-phenylenediamine	$10^{-9.4}$

*First constant.

The stability of the hydriodides of the tetraalkyl derivatives of o-phenylenediamine toward $CaCO_3$ (when compared with the corresponding m- and p-phenylenediamine derivatives) caused us to postulate that the tetramethyl-, and also the tetraethyl-o-phenylenediamines possess a high basicity.

This postulation is fully confirmed by the values of the dissociation constants (see table), which were measured by S. P. Kozhevnikov and R. F. Mazel using the technique of potentiometric titration with a glass electrode at 20° in a solution containing 75% alcohol by volume.

From the data in the table it can be seen that replacing the four hydrogen atoms in the amino groups of o-phenylenediamine by either methyl or ethyl radicals leads to an increase in the dissociation constant of approximately 100 and 1000 times, respectively, whereas the tetramethyl-m-phenylenediamine has practically the same basicity as m-phenylenediamine.

A sharp increase in the basicity, occurring when o-phenylenediamine is ethylated or methylated, is apparently explained by steric hindrance. The dialkylamino groups in alkylated o-phenylenediamine, found ortho to each other, cannot fit in the plane of the benzene ring, and for this reason the axes of the p-electrons of the nitrogen atoms and of the π-electrons of the benzene ring are no longer found in parallel. This leads to a weakening of the mutual effect between the benzene ring and the dialkylamino groups, and consequently to an increase in the value of the dissociation constant of the ortho-ditertiary base.

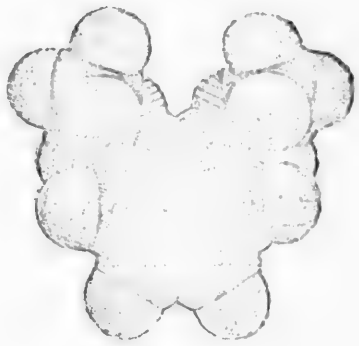


Fig. 1.

Stuart models of tetramethyl-o-phenylenediamine are shown in Figs. 1 and 2. The C atoms are black, the H atoms are white, and the N atoms are striped. The position of the $N(CH_3)_2$ groups when their conjugation with the benzene ring is most disturbed is shown in Fig. 1; here the axes of the p-electrons of the nitrogen atoms and of the π-electrons of the benzene ring are perpendicular to each other. Fig. 2 shows that turning both $N(CH_3)_2$ groups by 90°, necessary to achieve a parallel alignment of the indicated axes, is impossible due to steric hindrance. From these considerations it could be expected that the benzene ring in the tetraethyl- and tetramethyl-o-phenylenediamine molecules will show a lower reactivity toward those electrophilic reagents that react readily with aromatic amines. Employing the same conditions in all cases, we ran some experiments on the azo-coupling of the p-, m- and o-isomers of tetramethylphenylenediamine. It proved that in acetic acid medium both the p- and the m-isomer react immediately with p-nitrodiazobenzene to form dark purple azo dyes, in which connection the first of them remains in solution, while the second separates out as a precipitate. The nitrosation of tetramethyl-m-phenylenediamine in hydrochloric acid solution proceeds with the same ease, in which connection a brownish-red nitroso compound is formed. Under the same conditions, the tetramethyl-o-phenylenediamine fails to enter into either the azo-coupling or the nitrosation reaction. After making it alkaline the unreacted tetramethyl-o-phenylenediamine is recovered from the reaction mixture by extraction with ether.

We also attempted to azo-couple tetraethyl-o-phenylenediamine with p-nitrodiazobenzene. However, it proved that also in this case the azo-coupling reaction failed to go.

The obtained compounds were tested pharmacologically by Yu. I. Lisunkin [4]. Here it proved that the trimethyl-p-dimethylaminophenylammonium iodide, similar to ephedrine, raises the blood pressure and therefore is a member of a new class of ephedrinelike compounds.

Fig. 2.

EXPERIMENTAL

p-Phenylenebis(trimethylammonium) iodide [5, 6]. A mixture of 2.16 g of p-phenylenediamine, 4.4 g of calcium carbonate, 20 ml of methyl alcohol, 12 ml of water and 10 ml (23 g) of methyl iodide was heated under reflux for 10 hr. The precipitate was filtered, washed with methyl alcohol, and recrystallized from 20 ml of water using 1.5 g of activated carbon. The obtained product was filtered, washed with water, then with acetone, and dried in a vacuum-desiccator. Weight 6.6 g; at 230° the substance began to sublime gradually, especially between 262-266°, but it did not melt.

Found %: I 56.15, 56.19. $C_{12}H_{22}N_2I_2$. Calculated %: I 56.64.

The water was distilled from the filtrate in vacuo and the residue was treated with 20 ml of acetone. The precipitate was filtered, washed with acetone, and dried in a vacuum-desiccator. Another 1.4 g of substance was obtained, which decomposed in the same manner as described above when heated. The total yield of p-phenylenebis(trimethylammonium) iodide was 8 g (89.3%).

m-Phenylenebis(trimethylammonium) iodide [5]. A mixture of 2.16 g of m-phenylenediamine, 4.4 g of calcium carbonate, 20 ml of methyl alcohol, 5 ml of water and 10 ml (23 g) of methyl iodide was heated under reflux for 10 hr. The obtained precipitate (7.25 g) was recrystallized from dilute methyl alcohol (20 ml of alcohol + 5 ml of water) using 1.5 g of activated carbon. The product was filtered, washed with methyl alcohol, and dried in a vacuum-desiccator. We obtained 5.2 g (58.0%) of substance; the material on heating began to decompose, changing to a liquid at 185-187°.

Found %: I 55.84, 56.01. $C_{12}H_{22}N_2I_2$. Calculated %: I 56.64.

The original precipitate (7.25 g) can also be recrystallized from 12 ml of water using 1.5 g of activated carbon. Here the first crop weighed 3 g and an additional 3.1 g was obtained by evaporation of the filtrate and washing the dry residue with acetone. Total yield 68.1%.

Trimethyl-p-dimethylaminophenylammonium iodide [5, 6]. A solution of 2.25 g of p-phenylenebis(trimethylammonium) iodide and 0.7 g of KOH in 10 ml of water was heated under reflux for 4 hr. After cooling, the obtained precipitate was filtered, washed with water and with acetone, and then it was recrystallized from 20 ml of water. Yield 0.8 g (52%); the substance sublimes with decomposition at 272-275°.

Found %: I 41.15, 41.27. $C_{11}H_{19}N_2I$. Calculated %: I 41.45.

Tetramethyl-m-phenylenediamine [5]. Nine grams of m-phenylenebis(trimethylammonium) iodide was added to a solution of sodium alcoholate, prepared from 1.9 g of sodium metal and 60 ml of dry alcohol, and the mixture was boiled, using a reflux condenser connected to a calcium chloride tube, until all of the precipitate had dissolved (38 hr). Then most of the alcohol was removed by distillation. The residue was cooled and treated with 10 ml of water and 40 ml of ether. The ether solution was separated, washed with water, and dried over solid NaOH. After distilling off the ether the residue was distilled. Yield 2.4 g (63.8%); b.p. 166-169° at 51-53 mm.

Found %: C 72.86, 72.90; H 9.90, 9.85. $C_{10}H_{16}N_2$. Calculated %: C 73.12; H 9.82.

Trimethyl-m-dimethylaminophenylammonium iodide [5]. Method A. A solution of 1 ml of methyl iodide in 7 ml of acetone was added to a solution of 2.2 g of tetramethyl-m-phenylenediamine in 30 ml of distilled acetone. The obtained precipitate was filtered, washed with acetone, and recrystallized from 25 ml of dry ethyl alcohol using 0.6 g of activated carbon. Yield 2.9 g (70.7%); m.p. 188-190° (decompn.).

Found %: I 41.57, 41.47. $C_{11}H_{19}N_2I$. Calculated %: I 41.45.

Method B. A solution of 6.75 g of m-phenylenebis(trimethylammonium) iodide and 2.1 g of KOH in 30 ml of water was heated under reflux for 4 hr. An oily layer separated on the bottom of the flask when the solution was cooled, which was treated with 5 ml of water; the oily layer solidified on shaking. The obtained precipitate was filtered, washed with 5 ml of water, and then with alcohol. The aqueous alcohol was distilled from the filtrate in vacuo on the water bath. The residual precipitate was treated with 15 ml of dry alcohol (to remove traces of KOH and KI), the precipitate was filtered, and then it was heated under reflux with 20 ml of dry acetone, after which it was cooled and filtered again. Both precipitates were heated under reflux with 35 ml of dry alcohol, and the insoluble material [mainly m-phenylenebis(trimethylammonium) iodide] was filtered hot. Weight 1.2 g. The filtrate on cooling gave 2.5 g (54%) of trimethyl-m-dimethylaminophenylammonium iodide, m.p. 188-190° (decompn.).

Found %: I 41.38, 40.75. $C_{11}H_{19}N_2I$. Calculated %: I 41.45.

Tetramethyl-o-phenylenediamine hydriodide. A mixture of 10.8 g of o-phenylenediamine, 22 g of calcium carbonate, 135 ml of methyl alcohol, 45 ml of water and 50 ml (115 g) of methyl iodide was heated under reflux on the water bath for 10 hr. After cooling, the residue of calcium carbonate (7 g) was filtered and the filtrate was evaporated on the boiling water bath in vacuo. The residue was cooled, the thick mass was treated with 100 ml of dry acetone, and the mixture was shaken periodically. Here the calcium iodide gradually went into solution with the liberation of heat, while the reaction product remained as a crystalline precipitate. The latter was filtered, washed with dry acetone, and recrystallized from 60 ml of dry alcohol. We obtained 17.6 g (60.2%) of substance, m.p. 198-199°. The substance can be titrated with caustic solution in the presence of phenolphthalein.

Found %: C 40.54, 40.72; H 6.12, 6.09; N 9.63, 9.87; I 43.55, 43.43. $C_{10}H_{17}N_2I$. Calculated %: C 41.15; H 5.81; N 9.59; I 43.44.

Tetramethyl-o-phenylenediamine [2, 5]. A solution of 3 g of NaOH in 6 ml of water was added with cooling to a mixture of 10 g of tetramethyl-o-phenylenediamine hydriodide and 20 ml of water. The free base that separated here was extracted with 30 ml of ether, and the ether solution was washed, dried over fused sodium hydroxide, and after distilling off the ether the residue was vacuum-distilled. We obtained 5 g (89.2%) of substance with b.p. 103-106° at 32 mm. The material keeps well in a closed container.

Found %: N 17.42, 17.41. $C_{10}H_{16}N_2$. Calculated %: N 17.06.

Trimethyl-o-dimethylaminophenylammonium iodide. Method A [2]. Methyl iodide (13.2 ml; 30.3 g) was added to 4.4 g of distilled tetramethyl-o-phenylenediamine and the mixture was allowed to stand for 48 hr, after which the excess methyl iodide was vacuum-distilled, while the residue was recrystallized from 10 ml of dry alcohol in order to remove any tetramethyl-o-phenylenediamine. We obtained 4.9 g (60%) of substance, m.p. 210-212° (decompn.). The compound is soluble in water, but in insoluble in hot ether, benzene or dioxane. It does not titrate with caustic solution in the presence of phenolphthalein.

Found %: C 42.87, 42.90; H 6.37, 6.43; N 9.07, 8.96; I 40.95, 41.02. $C_{11}H_{19}N_2I$. Calculated %: C 43.31; H 6.25; N 9.15; I 41.45.

Method B. A mixture of 2.16 g of o-phenylenediamine, 20 ml of methyl alcohol, 12 ml of water, 4.4 g of calcium carbonate and 10 ml of methyl iodide was heated under reflux for 7 hr. The mixture after cooling was treated with 1.2 g of NaOH, and this mixture was refluxed for another 3 hr. The solution was separated from the precipitate by filtration, after which the aqueous methyl alcohol was carefully distilled from the filtrate, and the residue was treated with 20 ml of dry acetone. The mixture was shaken in order to dissolve the potassium iodide and then it was cooled, followed by filtration of the precipitate and its recrystallization from 8 ml of dry alcohol. We obtained 2.7 g (44.1%) of substance. The compound decomposes without melting at 210-212°. It does not titrate with caustic solution.

Tetraethyl-o-phenylenediamine hydriodide. A mixture of 5.4 g of o-phenylenediamine, 11 g of calcium carbonate, 50 ml of alcohol, 20 ml of water and 27 ml (52.1 g) of ethyl iodide was heated under reflux on the water bath for 10 hr. The calcium carbonate was filtered, and the alcohol and water were distilled from the filtrate in vacuo. After cooling, the residue was treated with 50 ml of dry acetone, and the obtained precipitate was filtered and washed with dry acetone. We obtained 9.5 g (54.6%) of substance, m.p. (crude salt) 172-174°. The compound is soluble in water and in alcohol, and insoluble in dry acetone and dry ether. It titrates with caustic solution.

Found %: C 47.85, 48.25; H 7.66, 7.59; N 8.08, 7.88; I 36.61, 36.63. $C_{14}H_{25}N_2I$. Calculated %: C 48.27; H 7.24; N 8.05; I 36.44.

To isolate the base [7] we shook 7 g of the salt with a solution of 2 g of NaOH in 30 ml of water, and the obtained oil was extracted with 30 ml of ether. The ether solution was washed with water, dried over fused potassium carbonate, and after distilling off the ether the residue was distilled. We obtained 3.5 g (84.5%) of the free base with b.p. 140° at 26-27 mm.

Found %: N 13.10, 13.11. $C_{14}H_{24}N_2$. Calculated %: N 12.71.

Reaction of p-nitrodiazobenzene with tetramethyl-m-, tetramethyl-o- and tetraethyl-o-phenylenediamines. A solution of 1.65 g of p-nitroaniline in 4.5 ml of concd. hydrochloric acid and 3 ml of water was prepared by heating, after which the solution was cooled in ice, and the obtained suspension of p-nitroaniline hydrochloride was diazotized under cooling with a solution of 0.9 g of sodium nitrite in 4.5 ml of water. The obtained yellow diazo solution was made up to a volume of 15 ml with water.

Reaction with tetramethyl-m-phenylenediamine. A mixture of 0.66 g of distilled tetramethyl-m-phenylenediamine and 2.3 g of crystalline sodium acetate was dissolved in 15 ml of acetic acid and 6 ml of water, and the obtained solution was treated at room temperature with 5 ml of the cooled diazo solution. A precipitate was formed. The reaction mass was diluted with 20 ml of water, and the precipitate was filtered and washed with water. The air-dried dark purple product weighed 1 g. The azo dye was not studied further.

Attempt to azo-couple tetramethyl-o-phenylenediamine. A mixture of 0.66 g of tetramethyl-o-phenylenediamine and 2.3 g of crystalline sodium acetate was dissolved in 15 ml of acetic acid and 6 ml of water, and the obtained solution was treated with 5 ml of the cooled diazo solution. This resulted in the vigorous evolution of nitrogen and the odor of nitrophenol could be detected. A small amount of tarry residue was removed by filtration, and the filtrate was neutralized with NaOH solution, followed by extraction with ether. The ether solution was treated with dilute hydrochloric acid, and the hydrochloric acid solution was neutralized with NaOH solution, followed by extraction with ether. Removal of the ether by distillation and cooling of the residue led to the isolation of 0.4 g of a colored oil, which had the characteristic odor of tetramethyl-o-phenylenediamine. With methyl iodide the substance forms trimethyl-o-dimethylaminophenylammonium iodide.

Attempt to azo-couple tetraethyl-o-phenylenediamine. A mixture of 0.9 g of tetraethyl-o-phenylenediamine and 2.3 g of crystalline sodium acetate was dissolved in 15 ml of acetic acid and 6 ml of water, and the obtained solution was treated with 5 ml of the cooled diazo solution. A dark brown solution was formed, nitrogen began to evolve vigorously, and the odor of nitrophenol appeared. The next day the small amount of tarry residue was removed by filtration. The same as in the case of tetramethyl-o-phenylenediamine, the formation of the dye was not observed.

Nitrosation of tetramethyl-m-phenylenediamine. A mixture of 5 g of ice and 1.4 ml of concd. hydrochloric acid was added to 0.82 g of tetramethyl-m-phenylenediamine, and the obtained solution was treated with a solution of 0.38 g of sodium nitrite in 2.5 ml of water. A gold-colored precipitate deposited immediately, which was filtered, washed with water, dissolved with heating in 20 ml of alcohol, and the filtrate after cooling was treated with 40 ml of ether. The obtained precipitate was filtered, washed with a mixture of alcohol and ether, and dried at 50°. Weight 0.85 g. This compound was not investigated further.

Attempt to nitrosate tetramethyl-o-phenylenediamine. A mixture of 12 g of ice and 3.5 ml of concd. hydrochloric acid was added to 2 g of tetramethyl-o-phenylenediamine, and the obtained solution was treated, with stirring and ice cooling, with a solution of 0.95 g of sodium nitrite in 3 ml of water. Nitrogen oxides were evolved as the sodium nitrite solution was added. The solution was filtered, and 4 g of NaOH was added to the

filtrate with cooling. After extraction with ether, drying, and removal of the ether by distillation we obtained 2 g of an oil with the characteristic odor of tetramethyl-o-phenylenediamine.

SUMMARY

1. It was found that tetramethyl-m-phenylenediamine has practically the same basicity as m-phenylenediamine. Both tetramethyl- and tetraethyl-o-phenylenediamine have a much higher basicity than does o-phenylenediamine.

2. The tetraalkyl derivatives of o-phenylenediamine show a much lower reactivity toward electrophilic reagents (azo-coupling and nitrosation).

3. The theory was expressed that steric hindrance is responsible for the high basicity shown by the tetraalkyl-o-phenylenediamines, their low reactivity toward the above indicated electrophilic reagents, and also their inability to convert to the salts of the bis-quaternary bases.

4. It was found that trimethyl-p-dimethylaminophenylammonium iodide has an ephedrinelike action.

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ALKYLATED AROMATIC AMINES

II. REACTION OF UNSYMMETRICAL DITERTIARY p-PHENYLENEDIAMINES WITH ALKYL IODIDES

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1805-1814,
June, 1960
Original article submitted May 13, 1959

In this paper we describe the preparation of some tertiary-quaternary and bis-quaternary amino derivatives of the benzene series by the reaction of ditertiary bases of p-phenylenediamine with alkyl iodides.

A similar reaction has not been studied in detail up to now, although it possesses definite interest, since it makes it possible to determine how the presence of various aliphatic radicals in the amino group affects its course. The formation of only one tertiary-quaternary compound is possible only in those cases where the starting ditertiary base is a symmetrically substituted phenylenediamine. The formation of two isomeric tertiary-quaternary compounds is theoretically possible in all of the other cases.

We selected the following compounds as the starting ditertiary bases: symmetrical N,N,N',N'-tetramethyl-p-phenylenediamine (I) and its unsymmetrical homologs: N,N,N'-trimethyl-N'-ethyl-p-phenylenediamine (II) and N,N-dimethyl-N',N'-diethyl-p-phenylenediamine (III). Methyl iodide and ethyl iodide served as the haloalkylating agents. The structure of the possible isomers is shown in Scheme 1.

In addition, with excess alkyl iodide the formation of the bis-quaternary compounds could be postulated, the ease of obtaining which depends on the reactivity of the formed tertiary-quaternary derivatives.

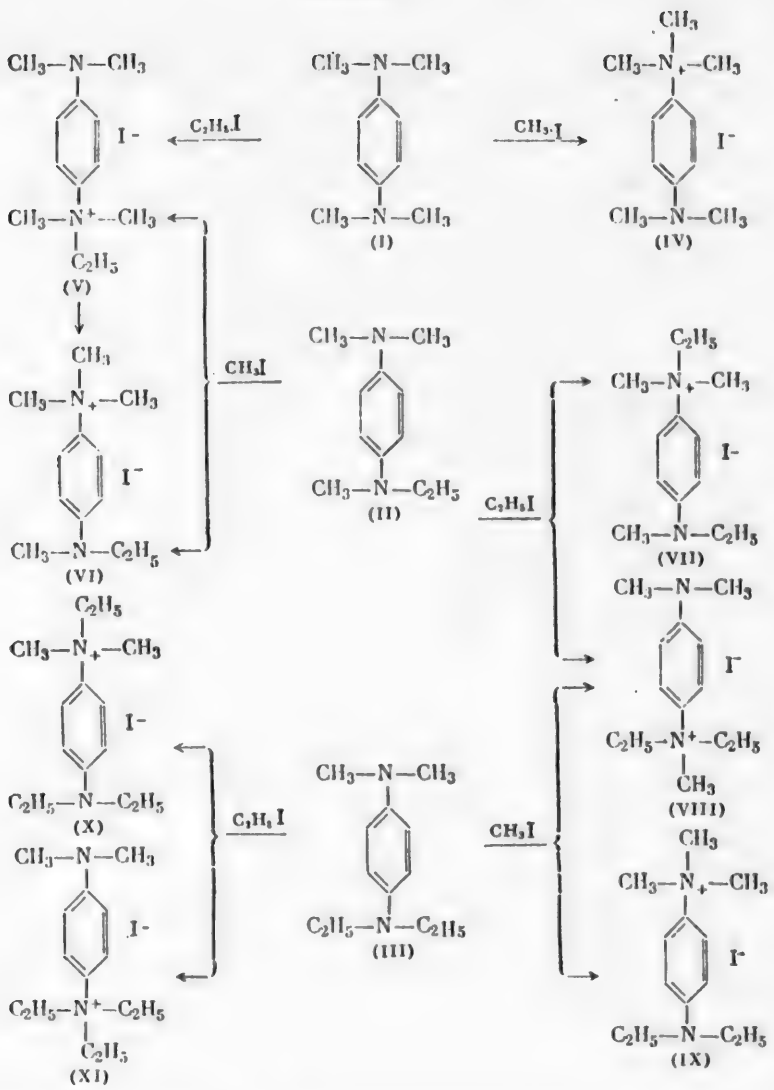
Of the p-phenylenediamines enumerated above the N,N,N'-trimethyl-N'-ethyl-p-phenylenediamine (II) is new, and we were the first to obtain it by the methylation of N-methyl-N-ethyl-p-phenylenediamine. To characterize (II) we prepared its picrate.

N-Methyl-N-ethyl-p-phenylenediamine was first obtained by Bent and co-workers [1], who give only its boiling point and the melting point of the sulfate $C_9H_{14}N_2 \cdot 1/2H_2SO_4$. We obtained the sulfate of this compound, having the composition: $C_9H_{14}N_2 \cdot H_2SO_4$, the melting point of which could not be determined. We also obtained the previously unknown picrate and picrolonate of N-methyl-N-ethyl-p-phenylenediamine, and also its acetyl and benzoyl derivatives.

The question of how the presence of different alkyls (methyls and ethyls) affects the reactivity of tertiary amino groups can be answered only by experiment. It is known that replacing the methyls by ethyls in a tertiary amino group causes the basic character of the amine to increase somewhat. Thus, for dimethylaniline, $K_B = 1.15 \times 10^{-9}$, while for diethylaniline, $K_B = 3.65 \times 10^{-8}$. In our case the ease of adding an alkyl, with a volume that is only slightly greater than that of hydrogen, could depend not only on the basicity of the tertiary amino group, but also on the size of the alkyl radicals already present in the given amino group.

As was revealed experimentally, reaction of the ditertiary p-phenylenediamines studied by us with one mole of alkyl halide proceeds best in dry acetone medium using a large excess (3 times the theoretical) of alkylating

Scheme 1



agent, at room temperature or under reflux. The formation of a mixture of isomers fails to occur under these conditions, and instead only one of the possible tertiary-quaternary compounds is formed. As a rule, the bis-quaternary derivatives are not formed here. This is apparently explained by the fact that in the tertiary-quaternary compound the formed quaternary ammonium group, because of its negative inductive effect, reduces the basicity of the tertiary amino group and in that way makes quaternization of the latter difficult.

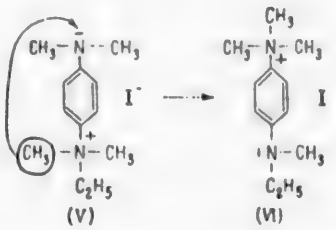
The above indicated choice of reactants made it possible to predict in advance the structure of some of the obtained tertiary-quaternary derivatives. Thus, the addition of a molecule of either methyl iodide or ethyl iodide to N,N,N',N'-tetramethyl-p-phenylenediamine gave trimethyl-(p-dimethylaminophenyl)ammonium iodide (IV) • and dimethylethyl-(p-dimethylaminophenyl)ammonium iodide (V), respectively. There is no doubt as to their structure.

The addition of methyl iodide to N,N,N'-trimethyl-N'-ethyl-p-phenylenediamine (II) gave only one compound, different in its properties (melting point, crystal form, solubility)** from substance (V). For this reason

• In our cases the usual naming of tertiary-quaternary compounds as being haloalkylates is unsuitable. For this reason we regard them as being quaternary derivatives of ammonium salts.

•• See Table 1.

we assigned it the structure of trimethyl-(p-methylethylaminophenyl)ammonium iodide (VI). It is interesting to mention that at elevated temperatures compound (V) is less stable than compound (VI): when (V) is heated in a sealed tube for 2 hr in an oil bath at 175° a substance appears in the exposed portion of the tube that in its properties and crystal form is identical with compound (VI).

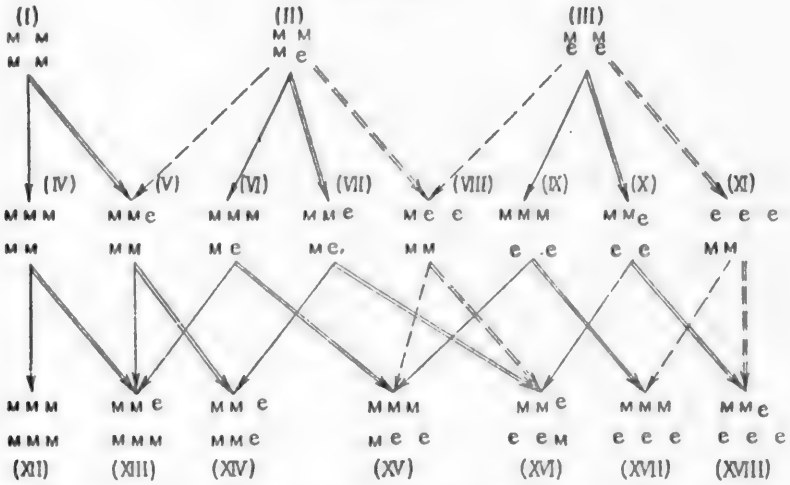


(V) (VI)

The greater stability of the quaternary ammonium group not containing an ethyl group, and also the addition of methyl to that tertiary amino group not containing an ethyl group, both indicate that in the investigated transformations the steric factor predominates over the basicity factor.

This postulation finds confirmation in other reactions of compounds (II) and (III) with methyl iodide and ethyl iodide (see Scheme 2). The reactions with methyl iodide are designated by single arrows in the scheme, while the reactions with ethyl iodide are designated by double arrows. Here the reactions that were actually achieved are designated by solid lines, while the reactions that could not be achieved are designated by dotted lines.

Scheme 2



Remarks. Arbitrary designations: m = methyl, and e = ethyl in alkylated p-phenylenediamines.

Because of the reduced reactivity of the tertiary amino group in tertiary-quaternary compounds, in order to obtain the bis-quaternary derivatives it was necessary to resort to drastic reaction conditions: the tertiary-quaternary derivatives were heated with a large excess of the alkyl iodide, without solvent, in a sealed tube for 8 hr at either 130° or 150°.

As was already mentioned, the structure of compounds (IV), (V) and (VI) is unequivocally determined by their synthesis. To determine the structures of (VII), (IX) and (X) we converted the obtained tertiary-quaternary compounds to the bis-quaternary compounds by adding a second molecule of alkyl halide (methyl iodide or ethyl iodide). The structure of all of the obtained bis-quaternary compounds is unequivocally determined by the starting reagents. For this reason a comparison of the obtained bis-quaternary compounds with each other makes it possible to unequivocally establish the structure of the starting tertiary-quaternary derivatives.

The reaction of methyl iodide with the compound having the structure of either (VII) or (VIII) yields p-phenylenebis(dimethylethylammonium) iodide (XIV), which we also obtained from dimethylethyl-(-p-dimethylaminophenyl)ammonium iodide (V) by reaction with ethyl iodide, and which cannot be obtained from isomer (VIII). This means that when N,N,N'-trimethyl-N'-ethyl-p-phenylenediamine (II) is reacted with ethyl iodide it is converted to dimethylethyl-(p-methylethylaminophenyl)ammonium iodide (VII), and not to its isomer (VIII).

Reaction of ethyl iodide with the compound having either structure (IX) or (VIII) [obtained from N,N-dimethyl-N',N'-diethyl-p-phenylenediamine (III) and methyl iodide] gives p-phenylene-N-trimethyl-N'-triethyldiammonium iodide (XVII), differing from compound (XVI), the structure of which was determined by its synthesis from (VII). This means that when base (III) is reacted with methyl iodide it forms trimethyl-(p-diethylaminophenyl)ammonium iodide (IX), and not isomer (VIII).

Finally, choosing between the two possible isomers (X) and (XI) (the compound that is obtained when N,N-dimethyl-N',N'-diethyl-p-phenylenediamine (III) is reacted with ethyl iodide) was done on the basis that when the compound was reacted with methyl iodide and when dimethylethyl-(p-methylethylaminophenyl)ammonium iodide (VII) was reacted with ethyl iodide we obtained the same substance (XVI) in both cases. This compound could not have been obtained from isomer (XI).

In addition to the above described bis-quaternary derivatives we obtained: p-phenylene-N-trimethyl-N'-methyldiethyldiammonium iodide (XV)• from two different tertiary-quaternary compounds (VI and IX), p-phenylene-N-trimethyl-N'-dimethylethyldiammonium iodide (XIII) from three different tertiary-quaternary compounds (IV, V and VI), and, finally, p-phenylenebis(trimethylammonium) iodide (XII)•• and p-phenylene-N-dimethylethyl-N'-triethyldiammonium iodide(XVIII) were obtained as the sole possible products of the addition of alkyl halide to the corresponding monoquaternary derivatives (IV and X).

As a result, we were able to confirm the fact that in the iodoalkylation of unsymmetrical ditertiary p-phenylenediamines the steric factor predominates over the basicity factor: the alkyl radical adds easiest to the tertiary amino group not containing ethyl radicals.

EXPERIMENTAL

I. Preparation of starting p-phenylenediamines. N,N,N',N'-Tetramethyl-p-phenylenediamine and N,N-dimethyl-N',N'-diethyl-p-phenylenediamine were obtained by the procedure described in the literature [4].

N,N,N'-Trimethyl-N'-ethyl-p-phenylenediamine was obtained from diethylaniline. Reaction of the latter with methyl iodide in dry acetone medium gave the iodomethylate (yield 93.2%), which was decomposed with sodium ethylate in anhydrous alcohol medium using the procedure of [5]. The yield of methylethylaniline was 62.75-67.2%, b.p. 204-205° at 758 mm. The isolated base was nitrosated in conventional manner. The yield of p-nitrosomethylethylaniline hydrochloride was 88.9-98.9%. Reduction to the amino derivative was done in hydrochloric acid medium using stannous chloride. The yield of amine hydrochloride was 82.5-89.2%. Methylation of the N-methyl-N-ethyl-p-phenylenediamine and separation of the reaction products was done in the same manner as has already been indicated for the alkylation products of p-aminodimethylaniline. The yield of N,N,N'-trimethyl-N'-ethyl-p-phenylenediamine was 23.6-41.7%, based on the p-aminomethylethylaniline hydrochloride.

N-Methyl-N-ethyl-p-phenylenediamine sulfate. Concentrated sulfuric acid was added in drops to a cooled solution of 1.1 g of the freshly distilled base in 10 ml of alcohol. The precipitate of amine salt was filtered, washed with alcohol, and dried in a vacuum-desiccator over calcium chloride. The compound was purified by recrystallization from alcohol. Cooling of the alcohol solution gave the sulfate as long white needles, which were rapidly filtered, washed with anhydrous alcohol, then with ether, and dried in a vacuum-desiccator over calcium chloride. The obtained sulfate proved to be so hygroscopic that we were unable to determine its melting point even in a sealed tube.

Found %: S 13.16, 13.10. $C_9H_{14}N_2 \cdot H_2SO_4$. Calculated %: S 12.91.

•Compound (XV) was obtained [2] in the methylation of N,N-dimethyl-N',N'-diethyl-p-phenylenediamine. The authors give m.p. 218°. Our m.p. 223-224°.

••Compound (XII) is reported in the literature [3].

N-Methyl-N-ethyl-p-phenylenediamine picrate was obtained by mixing hot alcohol solutions of 0.35 g of the free p-aminomethylethylaniline with a concentrated solution of either 0.53 or 1.07 g (1 or 2 equivalents) of picric acid. The mixture was boiled, cooled, and rubbing with a rod caused the monoacid salt to deposit as glistening leaflets. Recrystallization from 50% alcohol gave 0.78 g of orange crystals with m.p. 187-189°(decompn.).

Found %: C 47.43, 47.43; H 4.52, 4.43; N 18.81, 18.66. $C_{15}H_{17}O_7N_5$. Calculated %: C 47.49; H 4.52; N 18.47.

N-Methyl-N-ethyl-p-phenylenediamine picrolonate was obtained by mixing hot alcohol solutions of 0.35 g of the free p-aminomethylethylaniline with a concentrated solution of 0.62 g (1 equivalent) of picrolonic acid; the mixture was boiled and then cooled; recrystallization from alcohol gave the compound as fine elongated prisms with m.p. 172-173° (decompn.). The product is the monoacid salt, crystallizing with 0.5 mole of alcohol.

Found %: C 54.71; H 5.29; N 18.81, 18.85. $C_{19}H_{22}O_5N_6 \cdot 1/2\ C_2H_5OH$. Calculated %: C 54.91; H 5.76; N 19.21.

N-Methyl-N-ethyl-N'-acetyl-p-phenylenediamine. A mixture of 1.9 g of the free p-aminomethylethylaniline and 7 ml of glacial acetic acid was refluxed for 1 hr. The acetic acid was vacuum-distilled. The residual dark oil was rubbed with petroleum ether. The obtained light gray precipitate was recrystallized from a mixture of petroleum ether and benzene (10 : 1). The compound deposited either as a quickly crystallizing colorless oil or as glistening leaflets with m.p. 84-87°.•

Found %: N 14.43, 14.62. $C_{11}H_{16}ON_2$. Calculated %: N 14.57.

N-Methyl-N-ethyl-N'-diacetyl-p-phenylenediamine. A solution of 2.85 g of the free p-aminomethylethylaniline in 15 ml of acetic anhydride was heated on the boiling water bath for 2 hr, after which the acetic acid and excess acetic anhydride were removed by vacuum-distillation. The residue was treated with 20 ml of water to give an oil which crystallized rapidly when rubbed with a rod. The material was filtered and washed with water. After drying we obtained 1.88 g of product with m.p. 71-72°. Recrystallization from either benzine or petroleum ether gave the compound as fine white needles. As the analysis indicated, the compound is p-diacetylaminomethylethylaniline.

Found %: N 12.16, 12.25. $C_{13}H_{18}O_2N_2$. Calculated %: N 11.96.

The monoacetyl derivative was obtained from the diacetyl compound by heating 0.32 g of the latter with 10 ml of 10% sodium carbonate solution for 1 hr. The floating oil was extracted with benzene (8 ml) and the extract was dried over potassium carbonate. Removal of the solvent by distillation left 0.2 g of a yellow oil, which crystallized when allowed to stand for a week. Recrystallization from petroleum ether gave the compound as a light-colored oil that crystallized rapidly, m.p. 84-87°.

N-Methyl-N-ethyl-N'-benzoyl-p-phenylenediamine. The free p-aminomethylethylaniline (1.6 g) was mixed with 5 ml of dry pyridine and 1.5 ml (1.8 g; 20% excess) of benzoyl chloride. The mixture was heated on the boiling water bath for about 3 hr, after which it was poured into 25 ml of water. The obtained dark precipitate was filtered and repeatedly washed with water. We obtained 2.05 g (75.7%) of product with m.p. 183-184°. Recrystallization of the substance from alcohol using carbon gave 1.05 g of white, asbestoslike needles with m.p. 187-189.••

Found %: N 11.21, 11.14. $C_{16}H_{18}ON_2$. Calculated %: N 11.02.

N,N,N'-Trimethyl-N'-ethyl-p-phenylenediamine. When freshly distilled, the compound solidifies to colorless crystals that melt easily at about 20°. The compound darkens rapidly on storage. B.p. 121-122° at 7 mm; 90-91° at 2 mm.

Found %: N 16.22, 16.06. $C_{11}H_{18}N_2$. Calculated %: N 15.71.

N,N,N'-Trimethyl-N'-ethyl-p-phenylenediamine picrate was obtained by mixing hot alcohol solutions of 0.32 g of the free diamine and a concentrated solution of 0.41 g (1 equivalent) of picric acid. The mixture was boiled, and on cooling the diacid salt deposited as dark-colored crystals (0.58 g), which after recrystallization from alcohol gave 0.3 g of reddish-orange crystals with m.p. 136-137° (decompn.).

•According to [6]: m.p. 92°

••In [7] the m.p. is erroneously given as 135-136°.

TABLE 1

Compound No.	Name	Formula	Purification conditions and crystal form	Yield (%) before recrystallization	Yield (%) after recrystallization	Melting point	Found (%) N	Found (%) I	Calc. (%) N	Calc. (%) I
(IV)	Trimethyl-(p-dimethylaminophenyl)ammonium iodide*	$C_{11}H_{19}N_2I$	Recrystallization from alcohol, rhombic crystals	97.5	70.5	Sublimes without melting and with decomposition at 272–274°	9.32, 9.28	41.11, 41.17	9.06	41.07
(V)	Dimethylethyl-(p-dimethylaminophenyl) ammonium iodide	$C_{12}H_{21}N_2I$	Recrystallization from anhydrous alcohol, fine prisms	87.5	50.4		8.62, 8.90	39.45, 39.55	8.75	39.64
(VI)	Trimethyl(p-methylethylaminophenyl)ammonium iodide	$C_{12}H_{21}N_2I$	Recrystallization from alcohol, microscopic leaflets	94.5	65.2	Sublimes above 260° without melting	8.98, 9.04	39.68, 39.62	8.75	39.64
(VII)	Dimethylethyl-(p-methylethylaminophenyl)ammonium iodide	$C_{13}H_{23}N_2I$	Recrystallization from alcohol, needles	85.2	52.3	197—198°	7.73, 7.75	38.11, 38.07	8.38	37.98
(IX)	Trimethyl-(p-diethylaminophenyl)ammonium iodide	$C_{13}H_{23}N_2I$	Precipitation from anhydrous alcohol with dry ether, prisms	68.9	49.8	177—178°	8.23, 8.20	37.91, 37.76	8.38	37.98
(X)	Dimethylethyl-(p-diethylaminophenyl)ammonium iodide	$C_{14}H_{25}N_2I$	Recrystallization from dry acetone, rhombic crystals	78.8	28.1	180—181°	8.01, 8.08	36.31, 36.42	8.04	36.44

*Compound (IV) is reported in the literature [3].

TABLE 2

Compound No.	Name	Formula	Starting reagents	Yield (%) after recrystallization	Melting point	Crystal form	Found (%)		Calc. (%)	
							N	I	N	I
(XII)	p-(Phenylenebis(trimethylammonium) iodide	[illegible]	(IV) w.CH_3I	55.6	Sublimes above 240° without melting	Leaflets	6.25, 6.32	56.39, 56.47	6.25	56.64
(XIII)	p-Phenylene-N-trimethyl-N'-dimethylethyldiammonium iodide	$C_{13}H_{24}N_2I_2$	(IV) w.C_2H_5I (V) w.CH_3I (VI) w.CH_3I	32.5, 65.8, 52.7	Sublimes above 240° without melting	Flat prisms	6.24, 6.35	54.25, 54.31	6.06	54.92
(XIV)	p-Phenylenebis(dimethylethylammonium) iodide	$C_{14}H_{26}N_2I_2$	(V) w.C_2H_5I (VII) w.CH_3I	60.7, 35.1	Sublimes above 240° without melting	Leaflets	5.96, 6.01	53.42, 53.43	5.88	53.30
(XV)	p-Phenylene-N-trimethyl-N'-methyldiethyldiammonium iodide	$C_{14}H_{26}N_2I_2$	(VI) w.C_2H_5I (IX) w.CH_3I	43.8, 23.5		Long needles	6.00, 5.93	53.33, 53.29	5.88	53.30
(XVI)	p-Phenylene-N-dimethylethyl-N'-methyldiethyldiammonium iodide	$C_{15}H_{28}N_2I_2$	(VII) w.C_2H_5I (X) w.CH_3I	52.2, 25.6	234—235°	Long prisms	5.70, 5.73	51.58, 51.62	5.72	51.78
(XVII)	p-Phenylene-N-trimethyl-N'-triethyldiammonium iodide	$C_{15}H_{28}N_2I_2$	(IX) w.C_2H_5I	33.8	223—226°	Long prisms	5.77, 5.72	51.83, 51.54	5.72	51.78
(XVIII)	p-Phenylene-N-trimethyl-N'-triethyldiammonium iodide	$C_{16}H_{30}N_2I_2$	(X) w.C_2H_5I	27.9	216.5—217.5°	Microscopic prisms	5.69, 5.80	50.83, 50.88	5.56	50.34

Found %: N 17.84, 17.87. $C_{11}H_{18}N_2 \cdot 2C_6H_3O_7N_3$. Calculated %: N 18.02

N,N,N'-Trimethyl-N'-ethyl-p-phenylenediamine picrate. After separating the crystals of the diacid salt, the mother liquor was treated with an additional 0.41 g (1 equivalent) of picric acid; the mixture was boiled and then cooled. Here 0.2 g of yellow product deposited. Recrystallization from alcohol gave 0.1 g of the monoacid salt with m.p. 165-166° (decompn.).

Found %: N 13.95, 14.00. $C_{11}H_{18}N_2 \cdot C_6H_3O_7N_2 \cdot 2C_2H_5OH$. Calculated %: N 14.02.

II. The tertiary-quaternary derivatives of p-phenylenediamine were obtained by reacting 0.015 mole of the ditertiary base with 0.045 mole (3-fold excess)• of alkyl iodide in 5 ml of dry acetone.•• The reaction mixture was allowed to stand until morning,••• after which the precipitate was filtered, washed with dry acetone, then with ether, and dried. The compound was purified either by recrystallization from suitable solvent or by reprecipitation. All of the data are given in Table 1.

Isomerization of dimethylethyl-(p-dimethylaminophenyl)ammonium iodide to trimethyl-(p-methylethylaminophenyl)ammonium iodide. A charge of 0.2 g of dimethylethyl-(p-dimethylaminophenyl)ammonium iodide was sealed in a thick-walled tube and then heated in an oil bath at 175° for 2 hr. As heating progressed, a layer of white crystals formed on the inside portion of the tube extending above the surface of the oil. On conclusion of heating these crystals were carefully removed and then recrystallized from the minimum amount of alcohol using activated carbon. Here white leaflets of irregular shape were obtained, which sublimed without melting at a temperature above 250°, and proved to be identical with trimethyl-(p-methylethylaminophenyl)ammonium iodide.

III. Bis-quaternary derivatives of p-phenylenediamine. A charge of 0.00033 mole of p-phenylenediamine monoiodoalkylate and a 17-fold excess of alkyl iodide was sealed in a thick-walled tube and heated for 8 hr at 130° (iodomethylation) or at 150° (iodoethylation).•••• The dark-colored reaction products were dried and then recrystallized from aqueous alcohol. All of the data are given in Table 2.

SUMMARY

1. A study was made of the reaction of N,N,N',N'-tetramethyl-p-phenylenediamine, N,N,N'-trimethyl-N'-ethyl-p-phenylenediamine and N,N-dimethyl-N',N'-diethyl-p-phenylenediamine with methyl iodide and with ethyl iodide.

2. Under mild conditions (in dry acetone in the cold or at reflux), even with an excess of alkyl iodide, only the tertiary-quaternary salt is formed. Six tertiary-quaternary derivatives were prepared, of which five are new compounds.

3. When an unsymmetrical ditertiary base of p-phenylenediamine is reacted with an alkyl halide, the alkyl group adds to the amino group that has the smallest aliphatic radicals. Steric hindrance is responsible for the direction of the reaction in this case.

4. The heating of dimethylethyl-(p-dimethylaminophenyl)ammonium iodide causes isomerization, which consists in the shifting of the methyl radical of the quaternary dimethylethylammonium group to the tertiary dimethylamino group, with the formation of trimethyl-(p-methylethylaminophenyl)ammonium iodide.

5. Drastic conditions (at 130-150° under pressure) are required to add a second molecule of alkyl halide to the tertiary-quaternary derivatives.

6. By employing various techniques we synthesized seven bis-quaternary compounds, of which five are new. The bis-quaternary derivatives were used to prove the structure of the tertiary-quaternary compounds.

• We took equimolar amounts of the reactants to obtain the N,N,N',N'-tetramethyl-p-phenylenediamine derivatives.

•• The reaction does not go as well in wet acetone.

••• Iodoethylates (VII) and (X) were obtained by refluxing the reaction mixture for 1.5-1 hr.

•••• Ashley and Leeds [8] prepared some bis-quaternary derivatives, including (XII), from the monoiodoalkylates by heating with methyl iodide in a sealed tube at 100° for 72 hr in ethylene glycol medium.

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THE CYCLIZATION OF THE ETHYL ESTER OF N-CYANOETHYLGLYCINE

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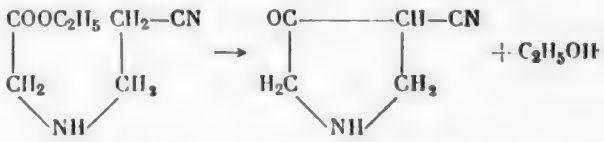
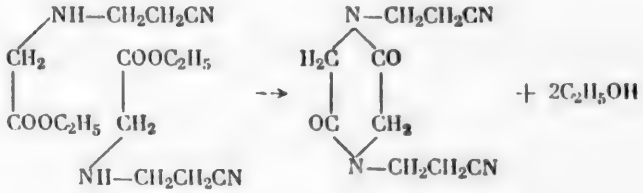
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1814-1816, June, 1960
Original article submitted June 6, 1959

In 1952 a paper was published by Cocker and co-workers [1] in which it was reported that heating the ethyl ester of N-cyanoethylglycine in benzene in the presence of sodium ethylate for 1 hr leads to the formation of 3-cyano-4-pyrrolidone in accordance with the scheme



However, the authors of this paper did not study the structure of the reaction product and limited themselves only to an analysis of the compound for carbon and hydrogen. According to the Irish scientists, 3-cyano-4-pyrrolidone has m.p. 165-166°.

Actually, when the ethyl ester of N-cyanoethylglycine was heated in the absence of both solvent and alkaline agent we obtained a substance with the same m.p. of 166°, the nitrogen analysis of which corresponded to the nitrogen content of 3-cyano-4-pyrrolidone. However, a more careful study of the reaction product revealed that the heating of the ethyl ester of N-cyanoethylglycine did not lead to the formation of 3-cyano-4-pyrrolidone, but instead to the formation of N,N'-dicyanoethyl-2,5-diketopiperazine. The cyclization proceeds in accordance with the scheme



Proof that the heating of the ethyl ester of N-cyanoethylglycine leads to the formation of N,N'-dicyanoethyl-2,5-diketopiperazine is the following: 1) the analysis data, both the calculated and the found for 3-cyano-4-pyrrolidone, are identical with the analysis data for N,N'-dicyanoethyl-2,5-diketopiperazine; the N,N'-dicyanoethyl-2,5-diketopiperazine obtained by us earlier by heating the methyl ester of N-cyanoethylglycine [2], and also by reacting acrylonitrile with 2,5-diketopiperazine [3], likewise has a m.p. of 166°; in this connection the mixed melting points of the cyclization product of ethyl N-cyanoethylglycinate with the N,N'-dicyanoethyl-2,5-diketopiperazines obtained by the other methods are not depressed; 3) the cyclization product of ethyl N-cyanoethylglycinate gives a positive reaction with picric acid; 4) hydrolysis of the cyclization product of ethyl N-cyanoethylglycinate, followed by esterification, leads to the formation of the ethyl ester of

N-carbethoxyethylglycine; the latter is also formed in the hydrolysis and subsequent esterification of the N,N'-dicyanoethyl-2,5-diketopiperazine [3] that is obtained by the cyanoethylation of 2,5-diketopiperazine; 5) trans-cyanoethylation occurs when the cyclization product of ethyl N-cyanoethylglycinate is heated with aniline in water in the presence of alkaline agents, and β-phenylaminopropionitrile can be isolated. The same trans-cyanoethylation product is also formed when aniline is reacted with the N,N'-dicyanoethyl-2,5-diketopiperazine obtained by the cyanoethylation of 2,5-diketopiperazine.

It should be mentioned that the cyclization of ethyl N-cyanoethylglycinate goes with much greater difficulty than does the cyclization of either ethyl glycinate or methyl N-cyanoethylglycinate.

EXPERIMENTAL

N,N'-Dicyanoethyl-2,5-diketopiperazine. Ten grams of the ethyl ester of N-cyanoethylglycine was heated at 110-120° for two weeks. The obtained thick, colored mass was treated with 20 ml of ethanol and then after standing in the refrigerator overnight it was filtered. The precipitate was boiled with carbon, recrystallized from water, and then washed with cold water, alcohol, and ether. Yield 1.4 g (20%). The substance gives a positive reaction with picric acid. The mixed melting points with the cyclization product of methyl N-cyanoethylglycinate and with the reaction product of acrylonitrile and 2,5-diketopiperazine were not depressed.

Found %: N 25.25, 25.39. $C_{10}H_{12}O_2N_4$. Calculated %: N 25.45.

Considerable tarring occurs when the ethyl ester of N-cyanoethylglycine is heated at a higher temperature.

Hydrolysis of the cyclization product of ethyl N-cyanoethylglycinate and subsequent esterification. The reaction was run in accordance with the procedure given in [3]. Here we obtained the ethyl ester of N-carbethoxyethylglycine with b.p. 249-251° (decompn.)(atmospheric pressure); 135-137° (9-10 mm); $n^{25}D$ 1.436; hydrochloride, m.p. 84-86°. The substance gives a negative ninhydrin reaction. The product obtained in the hydrolysis and subsequent esterification of the N,N'-dicyanoethyl-2,5-diketopiperazine obtained from the reaction of acrylonitrile with 2,5-diketopiperazine has the same constants [3].

Reaction of N,N'-dicyanoethyl-2,5-diketopiperazine with aniline. A mixture of 2.5 g of N,N'-dicyanoethyl-2,5-diketopiperazine, 9.3 g of aniline and 1 g of KOH (or 6 g of triethylamine) was heated in water (150 ml) under reflux for 20 hr. The procedure given in [4] was used to isolate the trans-cyanoethylation product. Traces of β-phenylaminopropionitrile were also isolated. M.p. 48-49°. Literature data: m.p. 49-50° [5].

The starting substance was recovered when the reaction was run in the absence of alkaline agents.

SUMMARY

The heating of the ethyl ester of N-cyanoethylglycine leads to the formation of N,N'-dicyanoethyl-2,5-diketopiperazine.

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β-BROMOPROPIONITRILE AS A CYANOETHYLATING AGENT

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1816-1818, June, 1960
Original article submitted June 6, 1959

Cyanoethylation employing acrylonitrile and β-chloropropionitrile is widely described in the literature, but up to now only one statement exists on the possibility of using β-bromopropionitrile for cyanoethylation [1]. In this paper we report the results of our experiments on the reaction of β-bromopropionitrile with amines and amino acids. The reaction proceeds in accordance with the scheme

$$R{-}NH_2 + Br{-}CH_2CH_2CN \rightarrow R{-}NH{-}CH_2CH_2CN + HBr.$$

The reaction of KOH, trimethylamine or triethylamine with β-bromopropionitrile leads to the formation of acrylonitrile.

EXPERIMENTAL

β-Diethylaminopropionitrile. Fifteen grams of diethylamine was added in drops, with stirring and strong cooling, to 20 g of β-bromopropionitrile. After heating under reflux for 2 hr the reaction mixture was treated with an aqueous solution of sodium hydroxide. The upper layer was separated from the bottom water layer. The water layer was then extracted several times with ether. The upper layer was added to the ether extracts, and the whole was then dried and distilled. Yield 17 g (90.4%).

B.p. 117-118° at 50 mm. Literature data: b.p. 112° at 45 mm [2]. The hydrochloride has m.p. 120° (from water), which agrees with the literature [2].

β-(N-Piperidyl)propionitrile. Fifteen grams of piperidine was added to 12 g of β-bromopropionitrile. The reaction conditions and the method used to isolate the cyanoethylation product were the same as in the preceding experiment. Yield 10.1 g (81.4%).

B.p. 128-129° at 30 mm. Methiodide, m.p. 153° (from methyl alcohol). Literature data: b.p. 114-115° at 18 mm; methiodide, m.p. 153° [3].

β-Phenylaminopropionitrile. A mixture of 2.7 g of β-bromopropionitrile and 9.3 g of aniline was heated in 150 ml of water under reflux for 10 hr. After adding 1.2 g of KOH, the reaction mixture was evaporated in vacuo to dryness. The residue was extracted with ether. The ether extract was evaporated until most of the solvent had been removed. The residual crude product was recrystallized from aqueous alcohol. Yield 2.3 g (80%). M.p. 49°. Literature data : m.p. 49-50° [4].

N-Cyanoethylglycine. Six grams of triethylamine was added to a solution of 2 g of glycine in 10 ml of water and then 4.4 g of β-bromopropionitrile was added gradually with cooling and stirring. After shaking for 2 hr and then allowing to stand overnight the solution was concentrated in vacuo to dryness. The dry residue was treated with 8-10 ml of water and then evaporated again to dryness. The solid residue was dissolved in a little water and the cyanoethylation product was precipitated by the addition of 95% alcohol. Yield 2.6 g (76.5%). M.p. 192-193° (decompn.). Literature data: m.p. 190-191° (decompn) [5]. The mixed melting points with the compounds obtained using either acrylonitrile or β-chloropropionitrile were not depressed.

Using β-bromopropionitrile, the products of the N-monocyanoethylation of alanine, α-aminobutyric acid, taurine, δ-aminovaleric acid and ε-aminocaproic acid were obtained in a similar manner.

N-Cyanoethyltyrosine. Two grams of tyrosine was treated with 10 ml of water and 2 g of KOH, and then 1.8 g of β-bromopropionitrile was added gradually with cooling and stirring. After shaking for 2 hr and then keeping overnight the reaction mixture was neutralized with hydrochloric acid. The precipitate of N-cyanoethyltyrosine obtained in this manner was filtered, washed with water, and then with alcohol. Yield 2.4 g (92.3%). M.p. 238-239° (decompn.), which agrees with the literature [5]. The mixed melting points with the products obtained using either acrylonitrile or β-chloropropionitrile were not depressed.

Using β-bromopropionitrile, the products of the N-monocyanoethylation of α-aminophenylacetic acid, β-phenyl-α-alanine, and β-phenyl-β-alanine were obtained in a similar manner, as was also N,N'-dicyanoethylcystine.

Reaction of potassium hydroxide or triethylamine with β-bromopropionitrile. The experiments were run under conditions similar to those used in the cyanoethylation of the amino acids with β-bromopropionitrile.
a) β-Bromopropionitrile (22 g) was added to a solution of 9.4 g of KOH in 30 ml of water. The upper layer was washed with a small amount of sodium chloride solution, after which it was dried over calcium chloride and distilled. The yield of acrylonitrile was 5.2 g (60%). B.p. 77-78°. Potassium bromide was isolated from the bottom water layer.

b) β-Bromopropionitrile (22 g) was added to a solution of 16.9 g of triethylamine in 30 ml of water. The upper layer was washed with weakly acidified water, then with a small amount of sodium chloride solution, after which it was dried over calcium chloride and distilled. Yield of acrylonitrile 5.2 g (60%). B.p. 77-78°. Triethylamine hydrobromide was isolated from the bottom water layer.

The reaction of β-bromopropionitrile with aqueous trimethylamine solution, and also with solid KOH, anhydrous trimethylamine or anhydrous triethylamine gave acrylonitrile in all cases in about 55-60% yield.

SUMMARY

β-Bromopropionitrile is an excellent agent for the cyanoethylation of amines and amino acids.

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CONJUGATED SYSTEMS

CXIX. THE DIRECTION OF ELECTROPHILIC ADDITION TO UNSYMMETRICAL DIENES. REACTION OF N,N-DIBROMOSULFONAMIDE WITH ALCOHOL SOLUTIONS OF DIVINYLACETYLENE AND ITS HOMOLOGS•

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1818-1823, June, 1960
Original article submitted June 29, 1959

In accordance with the electronic configuration of its molecule (in the stationary state), the hydration of vinylisopropenylacetylene (IV) should give the vinyl alkenyl ketone, but instead it gives isopropenyl allyl ketone, which isomerizes under the reaction conditions to isopropenyl propenyl ketone. Consequently, the hydroxyl group does not go to the most positively polarized quaternary carbon atom, but rather it goes to the third carbon atom [1]. In a similar manner the hydration of isopropenylmethylacetylene yields predominantly ethyl isopropenyl ketone [2]. At the same time both of the mentioned hydrocarbons have large dipole moments, apparently directed toward the first atom of the conjugated system [3, 4].

In order to experimentally determine the effect of the direction of polarization of unsymmetrical dienyne molecules on the order of addition of electrophilic reagents we investigated the reaction of three hydrocarbons in the C_nH_{2n-6} series (1,5-hexadien-3-yne, 2-methyl-1,5-hexadien-3-yne and 3-methyl-2,6-heptadien-4-yne) with N,N-dibromosulfonamide in methyl alcohol. The bromine atom fixed the point of initial electrophilic attack, and consequently the place of the greatest density of the electron cloud at the moment of reaction [5,6].

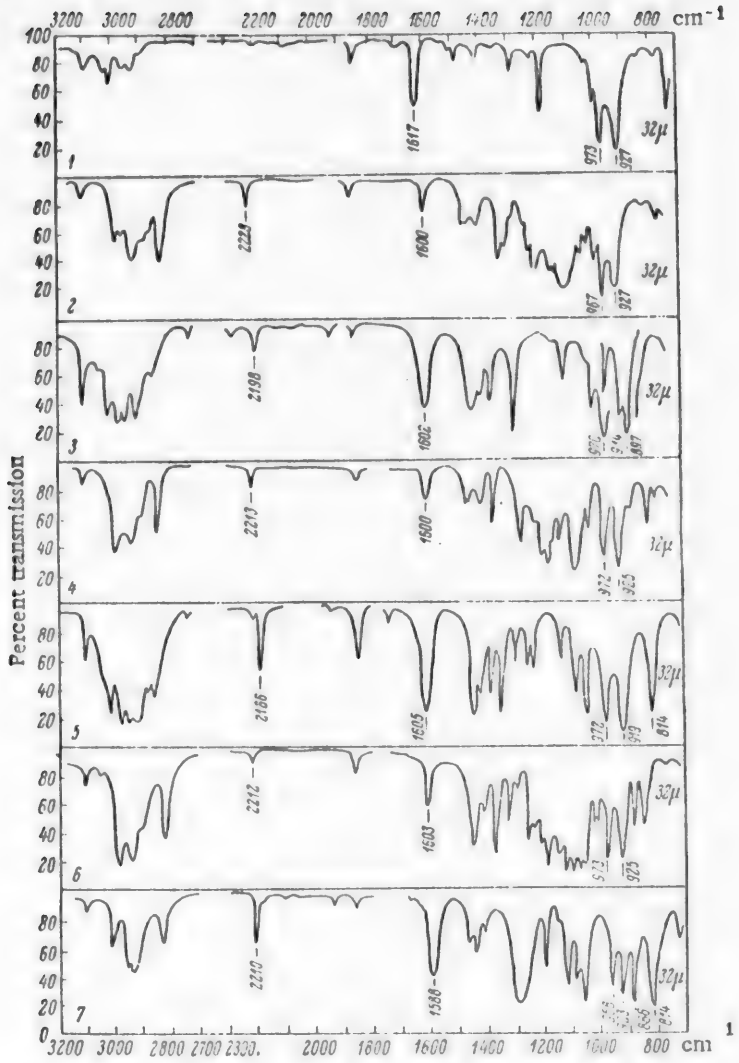
It had been shown earlier that vinylacetylenic hydrocarbons under these conditions add the elements of hypobromites predominantly at the ethylene linkage [7]. Consequently, only the formation of 1-bromo-2-methoxy-5-hexen-3-yne (II) could be expected when the reaction is run with unsubstituted divinylacetylene (I).

$$CH_2{=}CH{-}C{\equiv}C{-}CH{=}CH_2\ (I) \longrightarrow CH_2Br{-}CHOCH_3{-}C{\equiv}C{-}CH{=}CH_2\ (II) \longrightarrow$$
$$\longrightarrow CH_2{=}COCH_3{-}C{\equiv}C{-}CH{=}CH_2\ (III).$$

That the actually obtained bromoether had structure (II) was shown by several methods. The bromoether did not hydrolyze to the ketone when treated with dilute sulfuric acid in the cold, and consequently was not the enol ether, the methyl hypobromite adduct to the triple bond. When treated with alcoholic caustic solution the bromoether readily cleaved hydrogen bromide with the formation of the enol ether—methoxydivinylacetylene (III)—which on treatment with dilute sulfuric acid underwent hydrolysis with the formation of methyl vinylethynyl ketone (identified as the 2,4-dinitrophenylhydrazone).

The structures of both bromoether (II) and enol ether (III) were confirmed by studying their infrared spectra. The spectrum of the bromoether retained the frequencies of the vinyl group (967 and 927 cm^{-1}), which are also present in the spectrum of the starting divinylacetylene. The only difference is a slight shift in their location

•Dienynes. III. See [8] for Communication II.



Infrared transmission spectra. 1) 1,5-Hexadien-3-yne; 2) 1-bromo-2-methoxy-5-hexen-3-yne; 3) 2-methyl-1,5-hexadien-3-yne; 4) 1-bromo-2-methoxy-2-methyl-5-hexen-3-yne; 5) 3-methyl-2,6-heptadien-4-yne; 6) 2-bromo-3-methoxy-3-methyl-6-hepten-4-yne; 7) 2-methoxy-1,5-hexadien-3-yne.

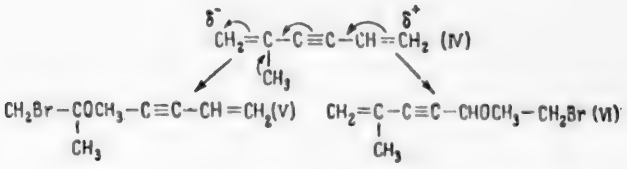
because of contraction of the conjugated chain. The frequencies of the substituted double bond were not detected (Figure, Curves 1 and 2). The infrared spectrum of methoxydivinylacetylene (III) showed the frequencies (2210, 1588, 972, 923, 814 cm^{-1}) characteristic for a substituted alkoxyl in the divinylacetylene system, observed earlier in the spectra of its homologs (Figure, Curve 7) [9].

As a result, there was no doubt but that the addition of methyl hypobromite to divinylacetylene proceeds predominantly (if not exclusively) at one of the equivalent double bonds. A. L. Klebanskii and co-workers [10] came to the same conclusion regarding the order of addition of ethyl hypochlorite to divinylacetylene.

Depending on the direction of shift of the electron cloud in the starting hydrocarbon molecule, when vinyl-isopropenylacetylene (IV) is reacted with N,N-dibromosulfonamide in methyl alcohol it could be expected that two adducts, obtained by addition to two differently constructed double bonds, would be formed (V and VI).

TABLE 1

Compound	Boiling point (pressure in mm)	d_4^{20}	n_D^{20}	MR found	MR calc.
$CH_2Br-CHOCH_3-C\equiv C-CH=CH_2$	91—92° (20)	1.3258	1.5108	42.70	41.47
$CH_2Br-CHOC_2H_5-C\equiv C-CH=CH_2$	85—86 (10)	1.2652	1.5030	47.45	46.08[9]
$CH_2Br-CHOC_4H_9-C\equiv C-CH=CH_2$	111—112 (10)	1.1784	1.4870	56.44	55.32[9]
$CH_2Br-C(CH_3)OCH_3-C\equiv C-CH=CH_2$	94—94.5 (20)	1.2734	1.5100	47.70	46.08
$CH_3-CHBr-C(CH_3)OCH_3-C\equiv C-CH=CH_2$	99—100(20)	1.2330	1.5051	52.24	50.70



The structure of the obtained bromoether was proved in the same manner as in the previous case. The substance proved to be stable toward both dilute acid and alcoholic caustic solution. These properties were compatible only with formula (V), which was confirmed by comparing the infrared spectra of the starting hydrocarbon and the bromoether.

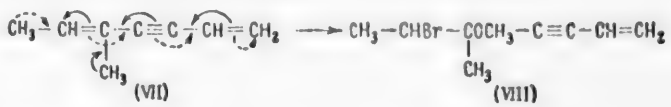
In the infrared spectrum of the starting hydrocarbon the frequencies at 914 and 970 cm^{-1} correspond to the CH-deformation vibrations in the vinyl group, while in the case of the isopropenyl group this frequency is at 897 cm^{-1}. The intense frequencies of the vinyl group (922 and 970 cm^{-1}) remain and the frequency at 897 cm^{-1} almost disappears in the spectrum of the bromoether. The frequencies at 2213 and 1603 cm^{-1} correspond to the conjugated system of multiple bonds in the bromoether. The frequencies characteristic for a bromine-substituted double bond are absent in the spectrum.

As a result, it was shown that vinylisopropenylacetylene adds methyl hypobromite at the isopropenyl group.

A similar order of methyl hypobromite addition was also observed when N,N-dibromobenzenesulfonamide was reacted with 3-methyl-2,6-heptadien-4-yne in methyl alcohol solution. Here we obtained bromoether (VIII), which proved to be stable toward both dilute sulfuric acid and alcoholic caustic solution.

The infrared spectrum of the bromoether showed frequencies characteristic for the vinyl group, while the frequency at 814 cm^{-1}, characteristic for the $-CH=C\langle$ grouping in the starting hydrocarbon, was absent (Figure, Curves 5 and 6).

As a result, only structure (VIII) can be assigned to the bromoether.



The presented experimental data show that the electrophilic addition of methyl hypobromite to vinylisopropenylacetylene proceeds in accordance with the postulated shift of the electron cloud in the molecule of this hydrocarbon under the influence of the methyl radical. In the case of 2-methyl-2,6-heptadien-4-yne the two methyl radicals act oppositely on the conjugated system. The experimentally established order of methyl hypobromite addition serves as evidence that the radical in the 3 position determines the polarization of the system. However, the possibility of the influence of other factors must also be taken into consideration in the given case, in particular, the high activity of the more highly substituted double bond in electrophilic addition reactions.

TABLE 2

Compound	Boiling point (10 mm)	d_4^{20}	n_D^{20}	MR	
				found	calc.
$CH_2{=}COCH_3{-}C{\equiv}C{-}CH{=}CH_2$	39–40°	0.9036	1.5076	35.65	33.23
$CH_2{=}COC_2H_5{-}C{\equiv}C{-}CH{=}CH_2$	52–52.5	0.8823	1.5010	40.79	37.85 [8]
$CH_2{=}COC_4H_9{-}C{\equiv}C{-}CH{=}CH_2$	81–82	0.8764	1.4928	49.79	47.09 [8]

A number of vinylacetylenic bromoethers were described as a result of the present investigation. The constants of these bromoethers are given in Table 1. From this table it can be seen that all of the bromoethers show an exaltation of the molecular refraction (about 1.3), which is characteristic for vinylacetylene systems. Both the specific gravity and the refractive index decrease when the length of the saturated radical in the ether grouping is increased.

A new member was also added to the β-alkoxydivinylacetylene series.

All of the known β-alkoxydivinylacetylenes are colorless liquids, showing a tendency to turn yellow and to polymerize when stored. From Table 2 it can be seen that they show a high molecular exaltation value (2.4-2.9).

EXPERIMENTAL

Bromomethoxylation of divinylacetylene. With good stirring and cooling (ice + salt), 14 g of N,N-dibromobenzenesulfonamide was added in small portions over a period of 3 hr to a solution of 7.7 g of divinylacetylene in 50 ml of methanol. The mixture was allowed to stand overnight, and then the bromoether was steam-distilled. Here we obtained 7 g (42%) of bromoether (II), with the constants given in Table 1.

Found %: C 44.58, 44.88; H 5.16, 5.16; Br 42.40, 42.80. C_7H_9OBr. Calculated %: C 44.47; H 4.80; Br 42.27.

When 4 g of bromoether (II) was heated with excess 10% KOH in methanol for 1 hr about 80% of the bromine contained in the sample went into solution. Steam-distillation of the solution led to the isolation of 1 g of methoxydivinylacetylene (III), with the constants given in Table 2.

Found %: C 77.03, 76.95; H 7.67, 7.60. C_7H_8O. Calculated %: C 77.75; H 7.46.

A solution of 0.2 g of methoxydivinylacetylene (III) in 10 ml of 5% sulfuric acid was added to an acetic acid solution of 2,4-dinitrophenylhydrazine. Here we obtained a precipitate of the 2,4-dinitrophenylhydrazone of methyl vinylethynyl ketone (5-hexen-3-yn-2-one) with m.p. 160° (from alcohol). A m.p. of 162° [9] was reported earlier for this compound.

Bromomethoxylation of vinylisopropenylacetylene. From 14 g of the hydrocarbon in 80 ml of methanol and 23 g of N,N-dibromobenzenesulfonamide under the earlier described conditions we obtained 16 g (54%) of bromoether (V), with the constants given in Table 1.

Found %: C 48.11, 48.10; H 5.60, 5.57; Br 39.67, 39.22. $C_8H_{11}OBr$. Calculated %: C 47.31; H 5.46; Br 39.35.

Five grams of bromoether (V) was heated for 1 hr with an equivalent amount of KOH in methanol solution, after which the reaction mixture was steam-distilled. Analysis of the aqueous solution remaining in the distillation flask revealed that about 4% of the bromine contained in the sample (V) was present as bromide ion. From the distillate we isolated 4.1 g (82%) of the starting bromoether (V), with b.p. 94-94.5° (20 mm), d^{20}_4 1.2689, $n^{20}D$ 1.5080.

Found %: Br 38.73, 38.70. $C_8H_{11}OBr$. Calculated %: Br 39.35.

Five grams of the bromoether was shaken for 7 hr with 5% sulfuric acid solution, after which the bromoether was separated from the aqueous layer and dried over $CaCl_2$. The frequencies of the carbonyl group could not be seen in the spectrum of the compound.

Bromomethoxylation of 3-methyl-2,6-heptadien-4-yne. From 30 g of the hydrocarbon in 200 ml of methanol and 46 g of N,N-dibromobenzenesulfonamide we obtained 45 g (70%) of bromoether (VIII), with the constants given in Table 1.

Found %: C 49.99, 50.10; H 6.26, 6.31; Br 36.62, 36.58. $C_9H_{13}OBr$. Calculated %: C 49.79; H 6.04; Br 36.81.

When a sample of the bromoether was treated with a 100% excess of 10% KOH solution in methanol, with heating on the water bath for 1 hr, about 6% of the bromine contained in the sample went into solution.

By operating as described above, we isolated from the solution the starting bromoether with b.p. 99-101° (20 mm), d^{20}_4 1.2287, $n^{20}D$ 1.5042.

Found %: Br 36.30, 36.36. $C_9H_{13}OBr$. Calculated %: Br 36.81.

When a sample of the bromoether was shaken with 5% sulfuric acid solution for 7 hr we were unable to detect the formation of any carbonyl compounds (established by the infrared spectrum).

SUMMARY

1. A study was made of the manner in which methyl hypobromite adds to divinylacetylene, vinylisopropenylacetylene and 3-methyl-2,6-heptadien-4-yne when solutions of these hydrocarbons in methanol are reacted with N,N-dibromobenzenesulfonamide.

2. It was established that the addition takes place at the double bonds, in which connection in the case of the last two hydrocarbons the addition is to the substituted vinyl group.

3. It was shown that the order of electrophilic addition to a dienyne system corresponds to its electronic configuration.

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POLYENE COMPOUNDS

XVII.* NEW SYNTHESIS OF 9,13-DIMETHYL-7-(1,1,5-TRIMETHYL-5-CYCLOHEXENYL)-7,9,11,13-NONATETRAEN-15-AL—RETINAL

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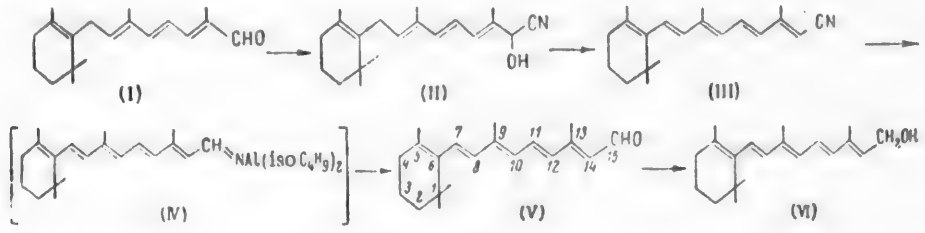
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1823-1828, June, 1960
Original article submitted May 13, 1959

The aldehyde corresponding to vitamin A, namely retinal (V), having all of the substituents attached to the double bonds in the trans-position, is characterized by showing the greatest biological activity [2] when compared with its three known mono-cis and one di-cis isomers. The ability to couple in vitro with the protein opsin and to form visual purple or rhodopsin [3, 4] was shown only by the 9,13-di-cis isomer [2] or neoretinal-b. Based on some more recent data, neoretinal-b is the 11-mono-cis isomer of the aldehyde corresponding to vitamin A [14]. In this connection trans-retinal, which in the organism takes part in the rhodopsin cycle, isomerizes to neoretinal-b.

The method described by us [1] for increasing the length of the chain by one carbon atom, with a transition from aldehydes with a discontinuous system of conjugation to aldehydes characterized by conjugation of all of the multiple bonds, was used in the present paper for the new synthesis of retinal. As the starting compound we used the accessible β-C_{19}-aldehyde [5] (I), in which connection we improved on the preparation of its acetals by using tetraethoxysilane, as is described in EXPERIMENTAL.



The reaction of β-C_{19}-aldehyde (I) with acetone cyanohydrin under the influence of methanolic KOH solution in the cold [6], and subsequent dehydration using phosphorus oxychloride and pyridine gave the nitrile of the acid corresponding to vitamin A (III) in 17% yield. When a solution of potassium cyanide and acetic acid in methanol [7] was used, the yield of chromatographically purified nitrile (III) was 68%. Reduction of the nitrile with diisobutylaluminum hydride and hydrolysis of the aldimine (IV) gave retinal (V) in very good yield.

The curves for the absorption of ultraviolet light by cyanohydrin (II), nitrile (III) and retinal are shown in Fig. 1. The properties of the retinal are in good agreement with those described earlier for this compound,

*See [1] for Communication XVI.

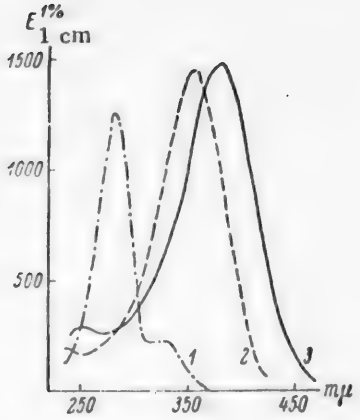


Fig. 1. Ultraviolet absorption spectra. 1) β-C_{19}-aldehyde cyanohydrin; 2) nitrile of the acid corresponding to vitamin A; 3) aldehyde corresponding to vitamin A or retinal.

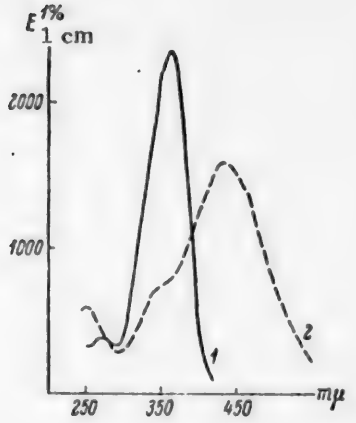


Fig. 2. Ultraviolet absorption spectra. 1) Semicarbazone of retinal; 2) 2,4-dinitrophenylhydrazone of retinal.

obtained by the oxidation of vitamin A [8-10], of β-carotene [11], or by synthesis [12, 13]. We repeated the oxidation of vitamin A using manganese dioxide and were convinced that the retinal, obtained by the different methods, had completely identical properties in all cases. The curves for the absorption of ultraviolet light by the semicarbazone and 2,4-dinitrophenylhydrazone of retinal are shown in Fig. 2.

The predominant formation of the trans-isomer serves as evidence that the tendency for trans-isomerization in the reduction reaction is greater than was observed in the synthesis of β-ionylideneacetaldehyde [1].

EXPERIMENTAL

1. 9,13-Dimethyl-7-(1,1,5-trimethyl-5-cyclohexenyl)-8,10,12-octatrien-14-al, β-C_{19}-aldehyde (I) [5]. To a solution of 5 g of β-C_{16}-aldehyde [5] (m.p. 76.5-77.2°) in 6.7 g of tetraethoxysilane (b.p. 165-167°, moisture content 0.088%) was added 0.25 g of orthophosphoric acid and 0.002 g of p-toluenesulfonic acid in 0.3 ml of anhydrous alcohol, after which the mixture was stirred and then allowed to stand in a nitrogen atmosphere at 20° for 3 days. The reaction mass was decomposed by adding 15 ml of ether and 17 ml of 15% NaOH solution. The ether layer was separated, and the aqueous layer was extracted with 20 ml of ether. The combined extracts were washed with 10 ml of water and then dried over potassium carbonate. The solvent was removed, and the residue was vacuum-distilled. Yield 6.33 g (96%).

B.p. 130-135° (0.05 mm), d^{20}_4 0.9376, $n^{20}D$ 1.5041, MR_D 96.58; calc. 94.245, ΔMR_D 2.33. UV-spectrum: λ_{max} (in ethanol) 237 mμ, $E^{1\%}_{1cm}$ 938.

Found %: C 78.48; H 11.18. $C_{22}H_{10}O_3$. Calculated %: C 78.37; H 11.18.

To 6.6 g of undistilled β-C_{16}-aldehyde diethyl acetal was added 0.2 ml of a 10% solution of zinc chloride in glacial acetic acid, and then 2.6 ml of ethyl propenyl ether (b.p. 69-70°) was added slowly at 25-30°. The reaction mass was stirred at 35-40° for 1 hr and then allowed to stand for 24 hr at 20°.

A mixture of 17.25 ml of acetic acid, 2.77 g of sodium acetate and 2.07 ml of water was added to the obtained ether-acetal. The reaction mass was heated slowly to 95-100° and then stirred at this temperature for 1 hr. Then it was cooled to 35-40° and poured over 100 g of crushed ice. After standing for 1 hr at 0° the obtained oil solidified to a hard yellow mass, which was filtered, washed first with 10 ml of cold sodium bicarbonate solution and then with 4 ml of water, and recrystallized from 16 ml of methanol. Yield 3.72 g (63.4%, based on the β-C_{16}-aldehyde).

M.p. 65.5-67°. UV-spectrum (in ethanol): λ_{max} 328 mμ, $E^{1\%}_{1cm}$ 1734.

Found %: C 83.64, 83.87; H 10.13, 10.10. $C_{19}H_{28}O$. Calculated %: C 83.77; H 10.36.

2. Cyanohydrin of 9,13-dimethyl-7-(1,1,5-trimethyl-5 cyclohexenyl)-8,10-12-octatrien-14-al (II).

a) To a solution of 10.47 g of sodium cyanide in 64.2 ml of anhydrous methanol, cooled to -20°, was added 5.76 g of C_{19}-aldehyde (m.p. 65-67°), and then 10 ml of glacial acetic acid in 1 hr. The mixture was stirred, allowing the temperature to rise gradually to 0° in 2 hr, and allowed to stand at -3 to -1° for 3 days. The pale yellow mass was mixed with methylene chloride (200 ml) with cooling (to 0°), and then it was washed with ice-cold water (2 x 30 ml) and dried over sodium sulfate. The solvent was removed at a temperature not exceeding 10°. We obtained 3.6 g (99.4%) of an oily orange substance.

UV-spectrum: λ_{max} (in ethanol) 278 mμ $E_{1\,cm}^{1\%}$ 1178.

Found %: act. H 0.329. $C_{20}H_{29}ON$. Calculated %: act. H 0.334.

b) Preparation of cyanohydrin of β-C_{19}-aldehyde using acetone cyanohydrin. A mixture of 1.36 g of β-C_{19}-aldehyde (m.p. 65-67°), 1.28 g of freshly distilled acetone cyanohydrin (b.p. 62-64° at 5 mm) and 0.03 ml of a saturated (at 20°) solution of KOH in methanol was allowed to stand at 20° for 5 hr (until all of the β-C_{19}-aldehyde had dissolved) and then at 0° for 12 hr. The reaction mass was dissolved in a 10-fold amount of chloroform cooled to 0°, then washed with cold water, and dried over sodium sulfate. The solvent was removed in vacuo to give 1.38 g (92.7%) of substance as a reddish oil.

Found %: N 3.97, 3.84; act. H 0.150. $C_{20}H_{29}ON$. Calculated %: N 4.67; act. H 0.334.

3. Nitrile of acid corresponding to vitamin A (III). A solution of 6.3 g of the β-C_{19}-aldehyde cyanohydrin in 12.6 ml of anhydrous pyridine was added in 5 min to a freshly distilled mixture of 4 ml of phosphorus oxychloride and 57.4 ml of pyridine. The temperature rose to 40-50° when the cyanohydrin was added. Then the mixture was heated under reflux with stirring for 1.5 hr, after which it was poured over crushed ice (100 g) and extracted with ether. The extract was washed with 5% sulfuric acid, then with sodium bicarbonate solution, and dried over sodium sulfate. The solvent was removed in vacuo, after which the residue (4.35 g, 73.4%) was dissolved in 5 ml of petroleum ether (40-60°) and chromatographed on 43.5 g of aluminum oxide (activity III). Leaching with petroleum ether (40-60°) containing 5% ethyl ether gave 100 ml of eluate, from which we isolated 4.1 g (69.3%) of the nitrile of the acid corresponding to vitamin A. The substance was obtained as a bright yellow viscous oil, showing intense absorption of ultraviolet light.

λ_{max} 358 mμ, $E_{1\,cm}^{1\%}$ 1480.

Found %: C 85.22, 85.25; H 9.46, 9.44; N 4.94, 4.68. $C_{20}H_{27}N$. Calculated %: C 85.35; H 9.67; N 4.98.

Without further purification, the β-C_{19}-aldehyde cyanohydrin obtained by method "b" was subjected to dehydration. Here we obtained 0.54 g of technical nitrile of the acid corresponding to vitamin A, which was dissolved in 2 ml of petroleum ether (40-60°) and chromatographed on 10.8 g of aluminum oxide (activity III). Elution with petroleum ether (40-60°) leached out the zone containing the free β-C_{19}-aldehyde (0.32 g), and then elution with petroleum ether containing 5% ethyl ether gave 30 ml of an eluate, which contained 0.18 g (16.72%) of the pure nitrile of the acid corresponding to vitamin A.

UV-spectrum (in ethanol): λ_{max} 358 mμ, $E_{1\,cm}^{1\%}$ 1480.

Found %: C 85.23; H 9.88; N 5.19, 4.94. $C_{20}H_{27}N$. Calculated %: C 85.35; H 9.67; N 4.98.

4. Aldehyde corresponding to vitamin A—retinal (V). A solution of 1.92 g of diisobutylaluminum hydride in 4.8 ml of anhydrous benzene was added dropwise in 30 min, with stirring, to a solution of 3.5 g of the nitrile of the acid corresponding to vitamin A in 10.5 ml of anhydrous benzene, cooled to 5°. After all of the hydride solution had been added the stirring was continued for another hour at 35°. The cooled reaction mass was gradually poured with stirring into 100 ml of 15% acetic acid at 5-6° in 1.5 hr. To decompose the aldimine the reaction mass was stirred for 15 min at 35°. The benzene layer was separated, and the water layer was extracted with benzene. The extract was washed with water, then with sodium bicarbonate solution, and dried over sodium sulfate. The solvent was removed in vacuo to give 3.46 g (98%) of residue, which was obtained as a reddish oil, devoid of nitrogen (based on the elemental analysis) and showing absorption of ultraviolet light (in ethanol): λ_{max} 376 mμ, $E_{1\,cm}^{1\%}$ 1220. A solution of 1.8 g of the technical retinal in 36 ml of dry petroleum ether (b.p. 40°) was cooled in 3 hr to -40°. The secondary products that separated here as a brownish precipitate (0.12 g) were filtered, after which the solution was concentrated to a volume of 10-12 ml and allowed to stand at -40° for 3 days. The retinal deposited as yellow-orange crystals weighing 0.84 g (46.7%). Two recrystallizations from petroleum ether (first 8 ml and then 5 ml), with gradual cooling from 0 to -40° in 2 hrs, gave 0.46 g of retinal as bright yellow crystals.

M.p. 56-57°. UV-spectrum (in ethanol): λ_{max} 381 mμ, $E^{1\%}_{1cm}$ 1475.

Found %: C 84.50, 84.45; H 9.95, 9.97. $C_{20}H_{28}O$. Calculated %: C 84.45; H 9.92.

The retinal prepared from crystalline vitamin A acetate (m.p. 57-58°) by saponification and subsequent oxidation with manganese dioxide has m.p. 55-57°; ultraviolet spectrum (in ethanol): λ_{max} 381 mμ, $E^{1\%}_{1cm}$ 1355.

Semicarbazone. We obtained 1.02 g (85.1%) of the semicarbazone from 1 g of the technical retinal. After two recrystallizations from ethanol (first 24 ml, and then 16 ml) we obtained 0.67 g (55.8%) of the semicarbazone of trans-retinal as glistening yellow plates. M.p. 193-193.5°. Ultraviolet spectrum (in ethanol): λ_{max} 375 mμ, $E^{1\%}_{1cm}$ 2360.

The mixed melting point with the semicarbazone of the trans-retinal isomer obtained by the oxidation of vitamin A, with m.p. 193-194°, was not depressed.

Found %: C 73.86, 74.14; H 9.04, 8.85; N 12.34, 12.14. $C_{21}H_{31}ON_3$. Calculated %: C 73.85; H 9.15; N 12.30.

2,4-Dinitrophenylhydrazone. A mixture of 0.5 g of the technical retinal in 13 ml of ethanol and 0.35 g of 2,4-dinitrophenylhydrazine was heated to the boil, after which 0.47 ml of concd. hydrochloric acid was added, and the whole was boiled for 15 min. Then the solution was cooled, after which the reddish-brown precipitate (0.8 g; 98.2%) was filtered, and then it was dissolved in 1.6 ml of chloroform and the solution was chromatographed on 40 g of aluminum oxide (activity III). Elution with chloroform first removed the lower broad zone of substance weighing 0.7 g, which was recrystallized from 39 ml of ethyl acetate. Reddish-brown crystals with a metallic luster. M.p. 214-215°. Ultraviolet spectrum (in ethanol): λ_{max} 448, 263 mμ, $E^{1\%}_{1cm}$ 1610, 590.

The mixed melting point with the 2,4-dinitrophenylhydrazone of the trans-retinal obtained from crystalline vitamin A acetate was not depressed.

Found %: C 67.22, 66.94; H 7.21, 7.17; N 11.87. $C_{26}H_{32}O_4N_4$. Calculated %: C 67.20; H 6.94; N 12.06.

9,13-Dimethyl-7-(1,1,5-trimethyl-5-cyclohexenyl)-7,9,11,13-nonatetraen-15-ol, vitamin A. A solution of 0.55 g of diisobutylaluminum hydride in 3.3 ml of benzene was added dropwise in 5 min at 4-6° to a solution of 1 g of retinal (λ_{max} 380 mμ, $E^{1\%}_{1cm}$ 1390) in 6 ml of dry benzene. The reaction mass was stirred for 30 min at 5° and another 20 min at 23-25°, cooled, and poured into 40 ml of 15% acetic acid at 2-5°. The stirring was continued at 5° for 30 min and then at 35° for 5 min. The benzene layer was separated, washed with a saturated water solution of sodium bicarbonate, and dried over sodium sulfate. The solvent was removed, and the residue was dried in vacuo at a temperature not exceeding 30°. We obtained 0.87 g of a viscous orange oil containing 0.75 g (86%) of vitamin A. Yield 82%. Crystalline vitamin A acetate was obtained by acetylation [15]. M.p. 56-57°. The yield was 0.45 g, or 84% based on the amount contained in the starting material.

Found %: C 80.14, 80.21; H 10.09, 10.07. $C_{22}H_{32}O_2$. Calculated %: C 80.43; H 9.82.

SUMMARY

1. The reaction of 9,13-dimethyl-7-(1,1,5-trimethyl-5-cyclohexenyl)-8,10,12-octatrien-14-al or β-C_{19}-aldehyde with potassium cyanide or acetone cyanohydrin gave the corresponding cyanohydrin, the dehydration of which gave the nitrile of the acid corresponding to vitamin A.

2. The reduction of the nitrile of the acid corresponding to vitamin A with diisobutylaluminum hydride, followed by hydrolysis of the obtained aldimine, gave 9,13-dimethyl-7-(1,1,5-trimethyl-5-cyclohexenyl)-7,9,11,13-nonatetraen-15-al, the aldehyde corresponding to vitamin A or retinal. The reduction of retinal gave vitamin A.

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SYNTHESIS OF THE ETHYL ESTER OF 4,6,9-TRIOXOCAPRIC ACID

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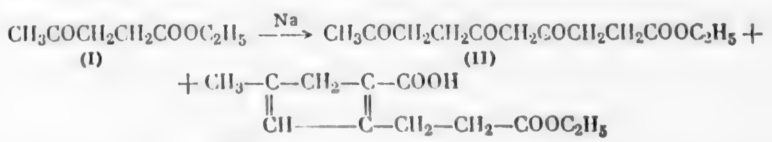
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1828-1831,
June, 1960
Original article submitted June 2, 1959

In studying the Claisen condensation of ethyl levulinate (I) we obtained the ethyl ester of 4,6,9-trioxocapric acid (II). We used sodium metal and lithium hydride as the condensing agents; the greatest yield was obtained using sodium. Besides the main reaction product, we isolated the ethyl ester of β-(4-methyl-2-carboxy-1,4-cyclopentadienyl)propionic acid (III).



(I) (II) (III)

Separation of the mixture of esters by fractional distillation in vacuo made it possible to obtain the pure ethyl ester of 4,6,9-trioxocapric acid (II), which previous authors were unable to accomplish.

Based on the existing papers on the subject, the possibility of the given condensation going is either rejected in general [1], or it is indicated that the reaction products are the ethyl ester of β-(4-methyl-2-carboxy-1,4-cyclopentadienyl)propionic acid (III) and the acid itself [2]; finally, in the paper published by the American investigators the ethyl ester of 4,6,9-trioxocapric acid, obtained as a by-product, was not isolated, and instead, without purification, was saponified to 4,6,9-trioxocapric acid [3].

It is the methyl and not the methylene group of the ethyl levulinate (I) that is chiefly involved in the condensation, which is proved by the absence of carbon dioxide evolution during the acid hydrolysis of ester (II), by obtaining 4,6,9-trioxocapric acid, and by determining the number of methyl groups attached to the carbon (by oxidation employing the Kuhn–L'Orsa method [4]). The results of determining the number of methyl groups in the ethyl ester of 4,6,9-trioxocapric acid coincide with the values found for the same groups in ethyl levulinate (I); consequently, the formation of isomers having a branched structure (IV and V) is excluded.

(IV) (V)

The ethyl ester of 4,6,9-trioxocapric acid (II) exists as a mixture of the keto and enol forms, which is confirmed by the results of titration with alkali, the molecular refraction value, the color obtained with an alcohol solution of ferric chloride, and the infrared absorption spectrum, in which a band at 1610 cm^{-1} is present, characteristic for enols [5].

The saponification of the ethyl ester of 4,6,9-trioxocapric acid (II) in acid medium gave 4,6,9-trioxocapric acid, proving to be the pure keto form, which is in harmony with the empirical rule of Meyer [6]; the material does not give a color with ferric chloride solution, and titrates only at the carboxyl group; the band corresponding to the enol form is absent in its infrared absorption spectrum.

It should be mentioned that in the preparation of derivatives of both the ester and the acid, involving the carbonyl groups, only the monophenylhydrazone and the monosemicarbazone are formed.

EXPERIMENTAL

Ethyl ester of 4,6,9-trioxocapric acid (II). Twenty grams of ethyl levulinate was added to 1.59 g of sodium wire in 100 ml of absolute ether. At first the reaction went at room temperature, then with heating, and was ended in 5 hr. The next day the sodium salt was separated and washed with 20 ml of absolute ether (the salt is hygroscopic). We recovered 5.12 g of unreacted ethyl levulinate from the ether solution. The salt was dissolved in 200 ml of ice water and then acidified with 15 ml of dilute (1 : 1) hydrochloric acid. The obtained oily substance was extracted with ether (3 × 50 ml) and the ether solution was dried over sodium sulfate. The ether was removed, and the residue (10.4 g) was vacuum-distilled.

The 1st fraction was the ethyl ester of 4,6,9-trioxocapric acid, a yellow oil that was soluble in alcohol, ether, chloroform, benzene, and dibromoethane. Yield 4.23 g (33.8%, based on reacted ethyl levulinate).

B.p. 164-170° (0.4 mm), $d^{22.4}_4$ 1.1419, $n^{22.4}D$ 1.4769, MR_D 59.92; calc. 59.50 (for keto form), 60.35 (for enol form).

Found %: C 59.52, 59.78; H 7.36, 7.48; CH_3 (by Kuhn–L'Orsa method) 6.86; enol form (titration with alkali) 38.2. M 245.5 (cryoscopically in dibromoethane). $C_{12}H_{18}O_5$. Calculated %: C 59.48; H 7.49; CH_3 12.37 (for two CH_3 groups). M 242.3.

The 2nd fraction was the ethyl ester of β-(4-methyl-2-carboxy-1,4-cyclopentadienyl)propionic acid, a viscous reddish-yellow liquid. Yield 0.6 g (3.84%). B.p. 197-205° (0.4 mm).

Found %: C 63.94; H 7.35. $C_{12}H_{16}O_4$. Calculated %: C 64.22; H 7.19.

When the condensation of ethyl levulinate was run in the presence of lithium hydride the yield of the ethyl ester of 4,6,9-trioxocapric acid was 13.5%.

The monophenylhydrazone of ethyl 4,6,9-trioxocaprate was obtained by heating 4 g of the ethyl trioxocaprate and 1.9 g of phenylhydrazine in 4 ml of methyl alcohol for 15 min. The next day the crystals were filtered, washed with 4 ml of methyl alcohol, and then recrystallized twice from methyl alcohol. Yield 1.7 g (31%). Colorless crystals, insoluble in water and in ether, and difficultly soluble in alcohol. M.p. 92-93°.

Found %: C 64.84; H 7.40; N 8.66. $C_{18}H_{24}O_4N_2$. Calculated %: C 65.03; H 7.28; N 8.42.

4,6,9-Trioxocapric acid. A solution of 5 g of ethyl 4,6,9-trioxocaprate in 10 ml of methyl alcohol was treated with 100 ml of dilute (1 : 2) hydrochloric acid. The mixture was heated under reflux for 24 hr. The hot hydrolyzate was treated with 0.5 g of activated carbon and filtered. The water was removed in vacuo, and the residue was recrystallized twice from ethyl acetate. Colorless crystals. Yield 1.5 g (34.1%) M.p. 116.5-118°.

Found %: C 56.10, 56.20; H 6.52, 6.78. Equiv. 213.8. $C_{10}H_{14}O_5$. Calculated %: C 56.07; H 6.59. Equiv. 214.0.

The monosemicarbazone of 4,6,9-trioxocapric acid was obtained by reacting a solution of 0.6 g of 4,6,9-trioxocapric acid in 10 ml of water with 1.5 ml of a semicarbazide solution, obtained by dissolving 10 g of semicarbazide hydrochloride and 10 g of potassium acetate in 30 ml of water. After 10-12 hr the crystals were filtered, washed with 5 ml of water, and then recrystallized twice from methyl alcohol. Colorless crystals. Yield 0.4 g (52.6%). M.p. 178.5-179.5°.

Found %: C 49.00, 48.56; H 6.62, 6.51; N 15.68, 15.70. $C_{11}H_{17}O_5N_3$. Calculated %: C 48.69; H 6.32; N 15.49.

SUMMARY

The ethyl ester of 4,6,9-trioxocapric acid was synthesized and its structure was proved.

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INVESTIGATIONS IN THE FIELD OF UNSYMMETRICAL α-OXIDES

II. PREPARATION AND PROPERTIES OF METHYLPHENYLETHYLENE, ETHYLPHENYLETHYLENE, METHYL-p-TOLYLETHYLENE, METHYLBENZYLETHYLENE, AND METHYLCYCLOHEXYLETHYLENE OXIDES

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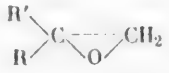
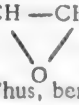
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1831-1837, June, 1960
Original article submitted June 29, 1959

In a previous communication [1] we presented some data on the effect of electron-donor substituents on the reaction of unsymmetrical oxides of the type



It has been established that the accumulation of methyl radicals leads to a decrease in the stability of the oxide ring. It was of interest to determine the effect of aromatic and aliphatic-aromatic radicals on the reactivity of unsymmetrical α-oxides. For this purpose we synthesized the unsymmetrical methylphenylethylene, ethylphenylethylene, methyl-p-tolylethylene, methylbenzylethylene, and methylcyclohexylethylene oxides. In almost all of the oxides mentioned one of the radicals is methyl, which makes it possible to compare the effect of the second radical on isomerization, hydration, and hydroxyamine formation.

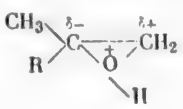
Many investigators [2] have established that mono- and unsymmetrical disubstituted ethylene oxides usually are isomerized to aldehydes. Isomerization takes place easily with radicals of the aliphatic series. It also is known that monosubstituted α-oxides of the type $C_6H_5(CH_2)n-CH—CH_2$ are isomerized with great difficulty.



Our experimental data in the main conform with these rules. Thus, benzylmethylethylene oxide is isomerized with more difficulty than the other oxides considered in this paper and forms a mixture of aldehyde and ketone.

At the same time, methyltolylethylene oxide is easily isomerized to aldehyde not only in the presence of acids, but even on distillation.

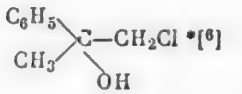
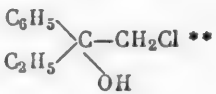
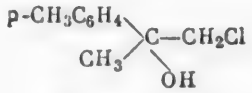
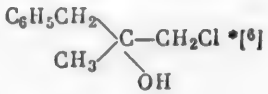
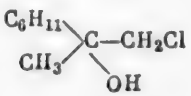
From the distribution of electron density in the unsymmetrical oxides it follows that the density of the electron cloud will be greatest near the tertiary carbon atom. In acid medium isomerization in all probability proceeds through the formation of an oxonium compound of the type



with subsequent rupture of the more polarized bond between the oxygen and the tertiary carbon atom. This will be promoted by the greater electron density at the tertiary carbon atom of the oxide ring as a result of the accumulation of electron-donor substituents, which can be arranged in series according to their effect: $p\text{-}CH_3C_6H_4 > C_6H_{11} > C_6H_5 > C_6H_5CH_2$.

TABLE 1

Chlorohydrins

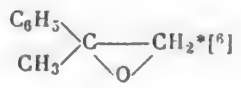
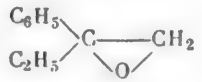
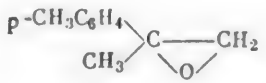
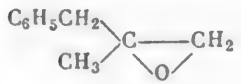
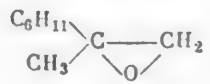
Expt. No.	Formula of chlorohydrin	Boiling point (pressure in mm)	d_4^{20}	n_D^{20}	MR_D		M		% Cl		Yield (%)
					found	calc.	found	calc.	found	calc.	
1		115—117° (15)	1.0431	1.5215	47.34	47.01	167.5	170.5	20.38	20.80	40—60
2		97—101 (5)	1.0770	—	—	—	180.2	184.5	18.90	19.20	45—60
3		120—121 (11)	1.0811	1.5250	52.22	51.66	186.0	184.5	19.40	19.20	30—40
4		155—156 (25)	1.0750	1.5190	51.94	51.66	180.5	184.5	19.00	19.20	42—45
5		48—50 (5)	0.9850	1.4730	50.11	49.81	174.0	176.5	20.40	20.10	50—55

•Compounds described in the literature.

••Darkened instantaneously.

TABLE 2

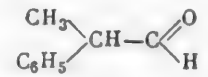
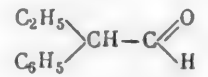
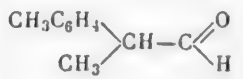
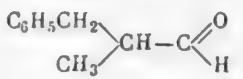
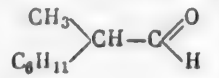
α-Oxides

Compound No.	α-Oxides	Boiling point (pressure in mm)	d_4^{20}	n_D^{20}	MR_D found	MR_D calc.	Found (%) C	Found (%) H	Calc. (%) C	Calc. (%) H	M found	M calc.	Yield of oxide (%)
(I)*		83—85° (15)	1.0280	1.5232	39.60	39.63	—	—	—	—	—	—	42—52
(II)		78—79 (6)	0.9982	1.5131	44.50	44.30	81.46	7.72	81.80	8.10	146.4	148.0	30—46
(III)		98—99 (10)	0.9978	1.5150	44.10	44.30	81.20	8.27	81.80	8.10	150.5	148.0	37—40
(IV)		85—86 (5)	0.9876	1.5083	44.12	44.30	81.34	7.89	81.80	8.10	146.0	148.0	30.5—32.0
(V)		78—80 (55)	0.9419	1.4680	41.00	41.12	76.80	12.0	77.10	11.80	142.0	140.0	38—46

*Compound described in the literature.

TABLE 3

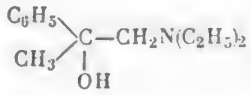
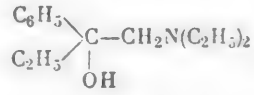
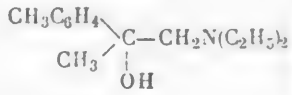
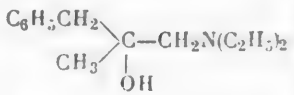
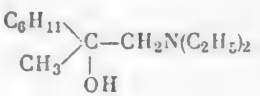
Carbonyl Compounds• [6]

No. of corresponding oxide	Name	Formula	Boiling point (pressure in mm)	d_4^{20}	n_D^{20}	Melting point of semicarbazone
(I)	2-Phenylpropanal		85—87° (10)	0.9980	1.5210	154—155°
(II)	2-Phenylbutanal		90—92 (10)	0.9965	1.5120	157—168
(III)	2-p-Tolylpropanal		88—89 (9)	0.9910	1.5165	159—160
(IV)	2-Benzylpropanal		226—227	0.9925	1.5110	70—72
	1-Phenylpropanone	$C_2H_5—CO—CH_2C_6H_5$	221—223	0.9970	—	152—153
(V)	2-Cyclohexylpropanal		75—78 (20)	—	1.4632	—

•All compounds described in the literature.

TABLE 4

Hydroxyamines

No. of corresponding oxide	Name	Formula	Boiling point (pressure in mm)	d_4^{20}	n_D^{20}	MR_D		M		% N		Yield (%)
						found	calc.	found	calc.	found	calc.	
(I)	1-Diethylamino-2-phenylpropanol-2		126—128° (17)	0.9410	1.5045	65.17	65.6	204.0	207.0	6.72	6.76	40—60
(II)	1-Diethylamino-2-phenylbutanol-2		115—116 (7)	0.9509	1.5102	69.60	70.3	220.8	221.0	6.32	6.34	70—80
(III)	1-Diethylamino-2-tolylpropanol-2		96—97 (8)	0.9531	1.5170	70.10	70.30	216.5	221.0	6.10	6.32	78—85
(IV)	1-Diethylamino-2-benzylpropanol-2		90—93 (12)	0.9574	1.5180	70.09	70.30	219.5	221.0	6.20	6.32	50—58
(V)	1-Diethylamino-2-cyclohexylpropanol-2		85—87 (7)	0.9328	1.4660	—	—	208.0	213.0	6.48	6.50	70—80

Hydration of the oxides was carried out under various conditions in the presence of hydrogen chloride or sulfuric acid. A mixture of glycols and aldehydes was obtained from methylphenylethylene, methyl-p-tolylethylene, and methylbenzylethylene oxides in weak acid solution. The glycol of the first oxide had been described previously by S. N. Danilov [3]. The simultaneous formation of isomerization and hydration products is explained by the fact that both of these processes occur under the same conditions in the presence of dilute mineral acids. In both cases the intermediate products formed are oxonium compounds, which can react either with the rupture of the ring and subsequent migration of a hydrogen atom or radical (which leads to formation of a carbonyl compound), or with rupture of the ring and addition of water. It is well known that even the synthesis of the oxides is often accompanied by the production of isomeric aldehydes or ketones [4].

By reaction of the oxides with diethylamine we obtained the corresponding hydroxyamines, the yield of which, depending on the structure of the oxide, varied from 40 to 80%. The hydroxyamines were obtained merely by heating the components on a boiling water bath in sealed ampoules for 20-30 hr. The reaction followed Krasuskii's rule. By oxidation of 1-aminodiethyl-2-phenylpropanol-2 with lead tetraacetate by a method described in the literature [5], we obtained acetophenone.

EXPERIMENTAL

The α-oxides were prepared from the corresponding chlorohydrins by the action of an excess of potassium hydroxide. The halohydrins were synthesized by the Grignard reaction from chloroacetone and the halogen derivatives (bromobenzene, p-bromotoluene, benzyl chloride, cyclohexyl bromide). The properties of the chlorohydrins and the α-oxides that were synthesized are given in Tables 1 and 2.

Isomerization of the oxides. All of the oxides that were synthesized as described above were subjected to isomerization, which was carried out in the presence of one drop of 3-5% sulfuric acid solution. The reaction products were quickly steam-distilled and were extracted from the distillate with ether. After drying with sodium sulfate, the ether was distilled off and the residue was distilled at atmospheric pressure or in vacuum. Aldehydes or ketones were obtained, the properties of which corresponded with the data in the literature. A summary of them is given in Table 3.

Reaction of the oxides with water. Hydration of the oxides was carried out by the following method. Gaseous hydrogen chloride was passed into a mixture of 2-3 g of the oxide and 8 ml of water until there was an acid reaction (pH6). Then the reaction mixture was shaken for 6-8 hr at room temperature and the product was extracted with ether, dried with sodium sulfate, the ether was distilled off, and the residue was distilled. Only from oxide (III) (Table 2) was a small amount of methyl-p-tolylethylene glycol obtained with m.p. 38°, which agrees with the data in the literature [7]. The other oxides, under the indicated conditions, were isomerized to aldehydes or ketones. In connection with this, we carried out the hydration by a method described by S. N. Danilov [3]. As a result, we obtained from oxide (I) the unsymmetrical methylphenylethylene glycol with m.p. 44°, b.p. 149-150° (2 mm), and from oxide (IV) the unsymmetrical methylbenzylethylene glycol with m.p. 56-60°. The small amounts of the glycols obtained did not permit more detailed investigation of them.

Reaction of oxides with diethylamine. In an ampoule were placed 2.5-3 g of oxide, 5 g of diethylamine, and 1-2 ml of water. After the ampoule had been sealed, it was allowed to stand for 18-20 hr at room temperature, then it was heated on a boiling water bath for 20-30 hr. The ampoule was opened, the unreacted diethylamine was distilled off on the water bath, and the hydroxyamine was distilled in vacuum. The properties of the hydroxyamines are presented in Table 4.

SUMMARY

1. By the action of alkali hydroxides on the appropriate chlorohydrins, the unsymmetrical methylphenylethylene, ethylphenylethylene, methyl-p-tolylethylene, methylbenzylethylene, and methylcyclohexylethylene α-oxides were prepared, the last four of these compounds being described for the first time.

2. The oxides that were synthesized were subjected to isomerization and hydration, and hydroxyamines also were prepared from them by reaction with diethylamine.

3. It was established that all of the above-described oxides are isomerized very easily to aldehydes or ketones even at room temperature. As a result of this, it is possible to obtain the glycols only in weakly acid medium in the cold.

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REACTION OF CYANAMIDE WITH ETHYLENE OXIDE. V

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1837-1841, June, 1960
Original article submitted June 7, 1959

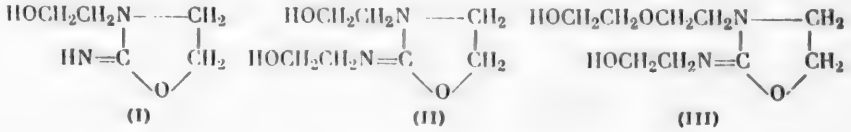
According to data in the literature and our previous investigations, ethylene oxide reacts with cyanamide to form monoethanolcyanamide and then 2-aminooxazoline [1-3]. Di-β,β'-dihydroxydiethylcyanamide also has been synthesized [4]. Fromm and his co-workers prepared 2-aminooxazoline, 2-amino-5-methyloxazoline, 5-methyl-2-aminooxazoline, and 5-chloromethyl-2-aminooxazolidine from alkylene oxides and also from the corresponding chlorohydrins with the sodium salts of cyanamide [5-8]. These compounds can be reacted both in the imine and in the tautomeric amine form.

We have studied the reaction of cyanamide with an excess of ethylene oxide in an autoclave with a stirrer at a comparatively low temperature. The reaction was carried out both in solvents, mainly in benzene, and without solvents. In all cases complex mixtures of derivatives of 2-iminooxazolidine were formed. It was not possible to separate the compounds by fractional distillation, since they decomposed on heating and changed in composition. At 200° and a residual pressure of 3 mm, only 35-40% of the material taken distilled. The remainder was converted, with the evolution of ammonia, to a solid tarry material.

To separate the mixture we used adsorption chromatography, employing potato starch as the sorbent, and chloroform, acetone, and methanol as the mobile solvents. The mixture to be separated and the starch were used in the ratio 1 : 4. The height of the column was 65 cm and the diameter 1 cm. The mixture was treated with chloroform and the dicyanamide was filtered off. The filtrate was introduced onto the chromatographic column and a third was eluted with chloroform. The mixture insoluble in chloroform was treated with hot acetone and the solution obtained was introduced onto the chromatographic column. Compound (II) was eluted with acetone. The residue was dissolved in methanol, introduced onto the same chromatographic column, and compound (I) was separated.

The following compounds were isolated and identified.

2-Imino-3-β-hydroxyethyloxazolidine-1,3 (I), 2-N-β-hydroxyethylimino-3-β-hydroxyethyloxazolidine-1,3 (II), and 2-N-β-hydroxyethylimino-3-(5'-hydroxy-3'-oxapentyl)oxazolidine-1,3 (III).



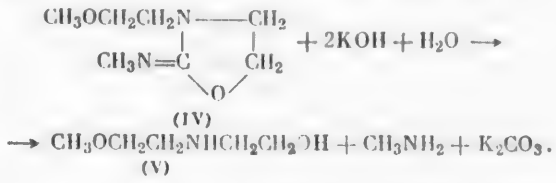
(I) (II) (III)

The composition and properties of the compounds prepared are given in Table 1.

All of the compounds were readily soluble in water and alcohol, insoluble in benzene and ether. Compound (III) was soluble in chloroform, acetone, and dioxane. When heated above 100°, they gradually decomposed. The structure of the compounds obtained was determined by hydrolysis of their ethers with 2.5% potassium hydroxide solution.

Compound	Empirical formula	% N		Equivalent		n_D^{20}	d_{20}^{20}	MR_D	
		calc.	found	calc.	found			calc.	found
(I)	$C_5H_{10}O_2N_2$	21.53	20.84	130	129	1.5210	1.2312	32.87	32.15
(II)	$C_7H_{14}O_3N_2$	16.09	16.26	174	172.5	1.5361	—	—	—
(III)	$C_9H_{18}O_4N_2$	12.84	12.64	218	219.2	1.5065	1.2210	54.51	53.10

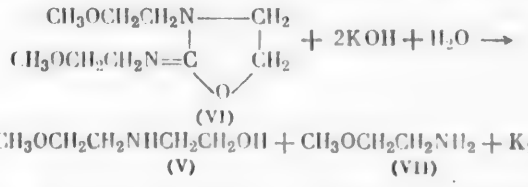
The cyclic structure of the first compound was confirmed by the fact that its methylation product (IV) had one methoxy group. When this ether was hydrolyzed, we obtained potassium carbonate, methylamine, and β-methoxy-β'-hydroxydiethylamine (V), which corresponds to the imine form:



(IV)

$$\longrightarrow \underset{(V)}{CH_3OCH_2CH_2NHCH_2CH_2OH} + CH_3NH_2 + K_2CO_3.$$

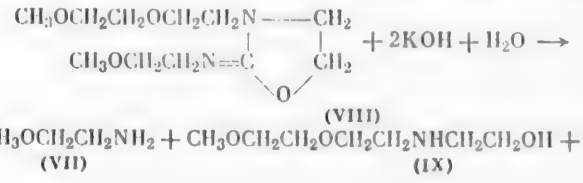
When the dimethyl ether of compound (VI) was hydrolyzed, β-methoxy-β'-hydroxydiethylamine (V), β-methoxyethylamine (VII), and potassium carbonate were obtained. This confirmed its imine form.



(VI)

$$\longrightarrow \underset{(V)}{CH_3OCH_2CH_2NHCH_2CH_2OH} + \underset{(VII)}{CH_3OCH_2CH_2NH_2} + K_2CO_3.$$

Hydrolysis of the dimethyl ether of the third compound (VIII) gave β-methoxyethylamine (VII) and 1-methoxy-8-hydroxy-3-oxa-6-azaoctane (IX), which is in conformity with its imine form.



(VIII)

$$\longrightarrow \underset{(VII)}{CH_3OCH_2CH_2NH_2} + \underset{(IX)}{CH_3OCH_2CH_2OCH_2CH_2NHCH_2CH_2OH} + K_2CO_3.$$

EXPERIMENTAL

A mixture of 0.5 mole of cyanamide, 1.1 mole of ethylene oxide, 75 ml of benzene, and 20 ml of calcium hydroxide were placed in an autoclave and heated with continuous stirring for 2.5 hr at 80-85°. After the reaction mixture had cooled, it was a viscous yellowish liquid. Yield 94-96%.

When the reaction was carried out at 70-75° the yield of the 1st fraction was 50%, of the 2nd 30%, of the 3rd 15%; at 90-95° the yield of compound (I) was 15%, (II) 50%, (III) 30%.

The reaction also took place even without a solvent: the mixture was stirred well and heated for 3 hr at 50-55°, with stirring for 5-6 min every 20-25 min. Yield 90-92%.

In order to separate the reaction products, we placed 12 g of the reaction mixture in a separatory funnel and treated it with 100 ml of chloroform in three portions. A considerable part of the mixture did not dissolve and floated on the surface. The chloroform solution was filtered and introduced onto a chromatographic column with starch. In this process compound (III) was eluted. The remaining mixture in the funnel was treated with small portions of 100-150 ml of hot acetone. The solution was filtered, introduced onto the same column with starch, and compound (II) was eluted. The material insoluble in acetone was dissolved in methanol, filtered, and introduced onto the column with starch, and compound (I) was eluted.

Complete elution of the individual fractions was determined by the refractive index and also by the change in their color (until the solvent was completely colorless).

Repeated examination of the materials separated on the chromatographic column confirmed their individuality and purity.

Preparation of Ethers from Compounds (I), (II), and (III).

In a flask with a reflux condenser were placed 0.05 mole of the compound under investigation, and 0.12 mole of dimethyl sulfate. The mixture was heated for 3 hr at 60-70°. After the reaction mixture had cooled, the unreacted materials were washed out with chloroform and acetone. The remaining mixture was dissolved in methanol and introduced onto a chromatographic column with silica gel, after which the ether was eluted with methanol. The ethers were obtained as viscous brown liquids, which appeared to be the salts of the ethers and methylsulfuric acid (X, XI, and XII).

Found %: N 9.98. Equiv. 266.7. $C_7H_{14}O_2N_2 \cdot CH_3OSO_3H$. Calculated %: N 10.37. Equiv. 270 (for salt of the ether of compound I).

Found %: N 8.87. Equiv. 304. $C_9H_{18}O_3N_2 \cdot CH_3OSO_3H$. Calculated %: N 8.91. Equiv. 314 (for salt of the ether of compound II).

Found %: N 7.72. Equiv. 352. $C_{11}H_{22}O_4N_2 \cdot CH_3OSO_3H$. Calculated %: N 7.82. Equiv. 358 (for salt of the ether of compound III).

The methylsulfuric acid in the compounds obtained was neutralized with 0.5 N potassium hydroxide solution and the water was distilled off. The mass remaining was dissolved in methanol and the potassium salt of the methylsulfuric acid was filtered off. After the methanol had been distilled off, the ether was isolated as a mobile yellowish liquid (XIII, XIV, and XV).

Found %: N 17.48; CH_3O 19.18. n^{25} 1.4858. $C_7H_{14}O_2N_2$ (XIII). Calculated %: N 17.72; CH_3O 19.62.

Found %: N 13.60; CH_3O 30.10. n^{18} 1.5085. $C_9H_{18}O_3N_2$ (XIV). Calculated %: N 13.86; CH_3O 30.68.

Found %: N 11.12; CH_3O 16.92. n^{28} 1.4790. $C_{11}H_{22}O_4N_2$ (XV). Calculated %: N 11.34; CH_3O 17.32.

Hydrolysis of ethers. In a flask with a reflux condenser were placed 0.05 mole of the ether and 250 ml of a 2.5% solution of calcium hydroxide. The mixture was heated for 3 hr at 90-95°. The methylamine and β-ethoxyethylamine obtained from the hydrolysis were steam-distilled off and titrated with 0.1 N hydrochloric acid solution, after which the distilled amines were isolated in the form of their hydrochlorides by evaporation. The presence of a primary amine group in them was established by the Van Slyke method and the isonitrile reaction. The residue of water in the distilling flask was distilled off, the remaining mixture was dissolved in acetone or methanol and the potassium carbonate was filtered off. To remove the residual potassium hydroxide, the filtrate was treated with carbon dioxide gas and the potassium carbonate was removed. The solvent was distilled off and the remaining mixture was dissolved in chloroform or acetone and introduced onto a column with silica gel. Compound (IX) was eluted with acetone, and compound (V) with methanol. The amines that were isolated were distilled in vacuum. β-Methoxy-β'-hydroxydiethylamine (V) distilled at 155-165° (3 mm), $n^{19.5}D$ 1.4692. 1-Methoxy-8-hydroxy-3-oxa-6-azaoctane (IX) distilled at 135-145° (3 mm), $n^{21}D$ 1.4780.

The distilled amines were yellowish liquids.

Found %: N 11.74; C 48.93; H 10.86; CH_3O 25.80. $C_5H_{13}O_2N$ (V). Calculated %: N 11.76; C 50.42; H 10.91; CH_3O 26.00.

Found %: N 8.69; CH_3O 19.2. M 167. $C_7H_{17}O_3N$ (IX). Calculated %: N 8.59; CH_3O 19.0. M 163.

Acetylation of compounds (V) and (IX). 0.03 mole of acetyl chloride was added drop by drop to 0.01 mole of compound (V) or (IX) with continuous stirring, after which the mixture was heated for 1 hr on a water bath. As a result of the reaction, compound (V) yielded the hydrochloride of 3-methoxy-β'-acetyldiethylamine, and (IX) the hydrochloride of 1-methoxy-8-acetyl-3-oxa-6-azaoctane as mobile yellowish liquid. The 1-methoxy-8-acetyl-3-oxa-6-azaoctane hydrochloride was removed from the reaction medium by extraction with butanol, and the β-methoxy-β'-acetyldiethylamine hydrochloride was removed by distillation in vacuum at 170-175° (2 mm). The hydrochlorides were titrated with 0.1 N alkali solution and their equivalents determined.

Found %: N 7.19. Equiv. 191.0. $C_7H_{15}O_3N \cdot HCl$. Calculated %: N 7.00. Equiv. 197.5.

Found %: N 6.37. Equiv. 233.8. $C_9H_{19}O_4N \cdot HCl$. Calculated %: N 6.21. Equiv. 241.5.

The structure of (V) and (IX) and also of their acetyl derivatives was confirmed by comparison with compounds synthesized by the methods given below. The presence of a secondary amine group was demonstrated by nitrosation.

Synthesis of β-methoxy-β'-hydroxydiethylamine (V). The compound was prepared by the action of dimethyl sulfate on diethanolamine. To 1 mole of diethanolamine was added drop by drop, with constant stirring, 0.5 mole of dimethyl sulfate, after which the mixture was heated for 1 hr on a water bath. The reaction mixture was neutralized with a 10% alcoholic solution of potassium hydroxide, centrifuged to remove the salt of methylsulfuric acid, and the amine was distilled off from the residue in vacuum at 167-175° (3-4 mm) in the form of a yellowish liquid, n^{21} 1.4689.

Found %: N 11.63. M 115. $C_5H_{13}O_2N$. Calculated %: N 11.76. M 119.

By reaction with acetyl chloride, the β-methoxy-β'-acetyldiethylamine hydrochloride that has been described was obtained.

Found %: N 7.31. Equiv. 193.7. $C_7H_{15}O_3N \cdot HCl$. Calculated %: N 7.00. Equiv. 197.5.

Synthesis of 1-methoxy-8-hydroxy-3-oxa-6-azaoctane (IX). To a mixture of 0.1 mole of compound (V) and 0.1 mole of ethylene chlorohydrin was added 0.12 mole of metallic sodium in small portions, with cooling, after which the mixture was heated for 1 hr on a water bath. The reaction products were treated with acetone, and the sodium chloride was removed by filtration, then the filtrate was introduced onto a column with silica gel and compound (IX) was eluted with acetone. After the solvent had been distilled off the compound was distilled in vacuum at 135-145° (3-4 mm) in the form of a colorless mobile liquid n^{21} 1.4760.

Found %: N 8.52. M 160.5. $C_7H_{17}O_3N$. Calculated %: N 8.59. M 163.

By acetylation with acetyl chloride the hydrochloride of 1-methoxy-8-acetyl-3-oxa-6-azaoctane was obtained.

Found %: N 6.24. Equiv. 237.3. $C_9H_{19}O_4N \cdot HCl$. Calculated %: N 6.21. Equiv. 241.5.

The amines that were synthesized were identical with those obtained by hydrolysis.

SUMMARY

1. When cyanamide was reacted with ethylene oxide, three compounds were obtained: 2-imino-3-β-hydroxyethyloxazolidine-1,3; 2-N-β-hydroxyethylimino-3-β-hydroxyethyloxazolidine-1,3; and 2-N-β-hydroxyethylimino-3-(5'-hydroxy-3'-oxapentyl)oxazolidine-1,3. Their properties, composition, and structure were determined.

2. A method was developed for the chromatographic separation of the compounds obtained.

3. It was demonstrated that all the compounds were derivatives of 2-iminooxazolidine.

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REARRANGEMENT OF HYDROXY- AND METHOXYBENZILS. II

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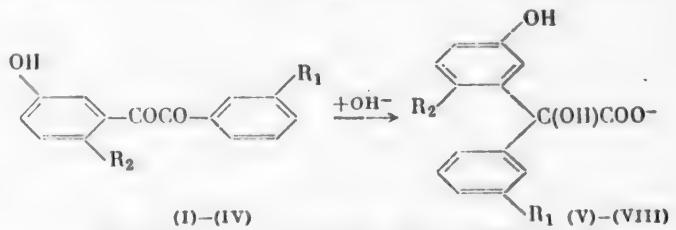
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1842-1848, June, 1960
Original article submitted June 9, 1959

In a previous communication [1] we described the rearrangement of hydroxybenzils containing hydroxyl groups in the ortho and para positions.

In the present investigation we studied the rearrangement of metahydroxybenzils.



(I)–(IV) (V)–(VIII)

(I), (V) $R_1 = H$, $R_2 = H$; (II), (VI) $R_1 = OH$, $R_2 = H$;
(III)–(VII) $R_1 = OCH_3$, $R_2 = H$; (IV), (VIII) $R_1 = H$, $R_2 = OCH_3$.

The hydroxybenzils (I) - (IV) were not previously known. To prepare them, 3-methoxy- and 3,3'- and 2,5-dimethoxybenzils were demethylated with pyridine hydrochloride or hydrobromic acid in a manner similar to that previously described for the other methoxybenzils [1]. The data relating to the starting methoxybenzils and the hydroxybenzils obtained from them are given in Table 1.

Splitting out one of the methoxy groups in 2,5-dimethoxybenzil might be assumed to produce 2-hydroxy-5-methoxy- or 5-hydroxy-2-methoxybenzil, or a mixture of them.

The hydroxymethoxybenzil obtained by us proved to be a single compound with a distinct melting point (103-104°). Selective demethylation of one of the two groups is possible only when there is a considerable difference in their reactivity. To determine the position of the hydroxy group in this product, we carried out the comparative demethylation with hydrobromic acid of 2,2'-, 3,3'-, 2,5-, and 4,4'-dimethoxybenzils under identical conditions. The results of the experiments, which are presented in Table 2, indicate the existence of a greater rate of demethylation of a meta-methoxy group in comparison with ortho- and para-methoxy groups.

The increased reactivity of the meta-methoxy group in demethylations with hydrohalogen acids has also been found, for example, in acetyl- and nitroanisoles [4]. The nature of the effect of meta-orienting substituents (in our case the group Ar–CO–CO is such a substituent) on the rate of dealkylation of alkylaryl esters of hydrogen-halogen acids is in agreement with the contemporary idea of the mechanism of this reaction [5].

The meta position of the hydroxy group in the benzil with m.p. 103-104° was confirmed also by the fact that the hydroxybenzilic acid obtained from it (see below) was stable, like other meta-hydroxybenzilic acids, and did not form a lactone. At the same time, all the ortho-hydroxybenzilic acids are unstable and easily form lactones [1].

TABLE 1

Methoxy- and Hydroxybenzils

Methoxybenzils	Melting point		Demethylating agent	Hydroxybenzils	Yield (in %)	Melting point (solvent for crystallization)	Empirical formula	Found (%)			Calc. (%)		
	our data	lit. data						C	H	H_{act}	C	H	H_{act}
3-Methoxy-	90—91° (from alcohol)	87—88° [2]	$C_5H_5N \cdot HCl$	3-Hydroxy- (I)	96.5	97—98° (benzene + hexane, CCl_4)	$C_{14}H_{10}O_3$	74.07, 74.84	4.53, 4.77	0.450, 0.449	74.32	4.46	0.446
3,3'-Dimethoxy-	82—83 (from alcohol)	82—83[2, 3]	$C_5H_5N \cdot HCl$	3,3'-Dihydroxy- (II)	92.0	149—149.5 (H_2O, dichloroethane)	$C_{14}H_{10}O_4$	69.01, 69.44	4.33, 4.32	0.824, 0.818	69.40	4.16	0.832
			HBr + acetic acid	3-Hydroxy-3'-methoxy- (III)	91.8**	68.5—69.5 (benzene)	$C_{15}H_{12}O_4$	70.67, 70.32	4.83, 4.99	0.403, 0.394	70.33	4.72	0.393
2,5-Dimethoxy*	97—98 (from benzene with hexane and from alcohol)	—	HBr + acetic acid	5-Hydroxy-2-methoxy- (IV)	95.5**	103—104 (benzene + hexane, H_2O, CCl_4)	$C_{15}H_{12}O_4$	70.57, 70.65	5.02, 4.85	0.400, 0.400	70.33	4.72	0.393

*Prepared for the first time. Found %: C 70.81, 71.15; H 5.59; H 5.56. $C_{16}H_{14}O_4$. Calculated %: C 71.09; H 5.22.

**Yields were calculated taking into account the dimethoxybenzil recovered from the reaction.

The hydroxybenzils (I)-(IV) rearranged readily and with good yields to the hydroxybenzilic acids (V)-(VIII) when they are boiled in aqueous alkali solutions. Some of the properties of these acids and their derivatives are given in Table 3. All of the acids were stable, at any rate under the conditions where ortho-hydroxybenzilic acids are converted to lactones (moderate heating, action of dilute mineral acids). The acids (V) and (VIII) crystallized readily, while (VI) and (VII) were obtained only as viscous sirups. 3-Hydroxy-(V), 3,3'-dihydroxy- (VI), and 3-hydroxy-3'-methoxybenzilic (VII) acids were characterized as the silver salts, from which crystalline methyl esters were obtained by treatment with methyl iodide.• When 3,3'-dihydroxy- (VI) and 5-hydroxy-2-methoxybenzilic (VIII) acids were methylated with dimethyl sulfate, we obtained 3,3'- and 2,5-dimethoxybenzilic acids, respectively, which were identified by a mixed melting point test with the compounds obtained by a known method.

TABLE 2

Comparative Demethylation of Dimethoxybenzils with Hydrobromic Acid

Demethylated dimethoxybenzil	2,2'-	3,3'-	2,5-	4,4'-
Yield of hydroxymethoxybenzil (in %)	25.4	52.8	55.0	26.4
Recovery of dimethoxybenzil (in %)	70.0	42.5	42.5	70.5

We have previously established that o-hydroxy- and dihydroxybenzils (2- and 2,2'-) rearrange more rapidly than the corresponding para isomers (4- and 4,4'-), and the monohydroxybenzils (2- and 4-) more rapidly than the corresponding dihydroxy derivatives (2,2'- and 4,4'-).

Comparison of the relative rates of conversion of the substituted benzils was continued in the present investigation. In Table 4 results are given for experiments in each of which the hydroxy- or methoxybenzils being compared were rearranged under identical conditions. Comparison of the relative rates of rearrangement of the methoxybenzils was of interest primarily in order to ascertain the nature of the ortho-effect in this case.

As would be expected on the basis of theoretical considerations and the data in the literature (for a brief summary see [1]), the m-hydroxy and m-methoxybenzils proved to be the most reactive in rearranging. Thus, the rate of conversion of the hydroxybenzils decreased according to the series meta > ortho > para. In the case of the methoxybenzils the ortho-effect proved to be normal and the rate changed according to the series meta > para > ortho.••

The rate of conversion of 3-hydroxybenzil, as for the other monohydroxybenzils, proved to be greater than for the corresponding dihydroxybenzil but less than for 3-methoxybenzil.

The 4-methoxy-, 2,2'-, 3,3'- and 4,4'-dimethoxybenzilic acids that were obtained in Expts. 6-8 (Table 4) had been described previously [6-8]. 2-Methoxybenzilic acid had been characterized only as a compound with two molecules of water [9], and the 3-methoxy acid was unknown. To identify all of these (and also the 2,5-dimethoxy-) acids we synthesized them specially from the corresponding benzils [6]. In Table 5 brief information is given on these acids.

EXPERIMENTAL

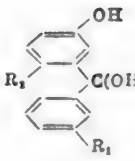
Methoxybenzils. 3,3'-Dimethoxybenzil was prepared from the corresponding benzoin [3] by the usual method [1]. 3-Methoxy- and 2,5-dimethoxybenzils were prepared from 3-methoxy- and 2,5-dimethoxyphenyl benzyl ketones, respectively, [10, 11] by oxidation with selenous acid in a manner similar to 2-methoxybenzil [1]. The yields were 88.5 and 97.5%, respectively.

Demethylation of methoxybenzils. 3-Hydroxy- and 3,3'-dihydroxybenzils were prepared from the corresponding methoxybenzils by heating (2 hr) with twice their weight of pyridine hydrochloride at 195-200° [1].

• The methyl esters of acids (VI) and (VII) crystallized only after prolonged storage (10-30 days) with periodic trituration.

••It should be noted, however, that the difference in the rates for the ortho and para isomers of the methoxybenzils probably is not so significant as in the case of the hydroxybenzils (compare Expts. No. 2 and 4 with Expts. 6 and 7, Table 4).

TABLE 3

Hydroxybenzilic Acids  and Their Methyl Esters

Compound No.	R_1	R_2	Yield (in %)	Melting point (solvent for crystallization)	Color with conc. H_2SO_4	Empirical formula	Found (%)			Calc. (%)		
							C	H	$H_{act.}$	C	H	$H_{act.}$
(V)*	H	H	95.3	149—151° (water)	Red violet	$C_{14}H_{12}O_4$	68.75, 68.76	5.39, 5.28	—	68.84	4.95	—
Methyl ester			93.5	102.5—104.5 (benzene + hexane)	Raspberry red (appeared gradually)	$C_{15}H_{14}O_4$	69.90, 69.80	5.68, 5.53	0.714, 0.704	69.77	5.46	0.780
(VI)*	OH	H	99.0	Did not crystallize	Gave no color	$C_{14}H_{12}O_5$	—	—	—	—	—	—
Methyl ester			93.0	157—159 (ether + hexane, di-n-butyl ether)	"	$C_{15}H_{14}O_5$	66.01, 66.18	5.28, 5.22	0.997, 0.995	65.69	5.14	1.103
(VII)*	OCH_3	H	91.7	Did not crystallize	"	$C_{15}H_{14}O_5$	—	—	—	—	—	—
Methyl ester			95.5	103—104 (benzene, dichloroethane)	"	$C_{16}H_{16}O_5$	67.10, 66.60	5.51, 5.90	0.655, 0.650	66.65	5.59	0.699
(VIII)	H	OCH_3	87.3	168 (decomp.) (water, dichloroethane)	Green	$C_{15}H_{14}O_5$	65.98, 65.89	5.11, 5.43	—	65.69	5.14	—

*Silver salts of the acids. (V). Found %: Ag 30.73, 30.68. $C_{14}H_{11}O_4Ag$. Calculated %: Ag 30.73. (VI). Found %: Ag 29.91, 29.97. $C_{14}H_{11}O_5Ag$. Calculated %: Ag 29.39. (VII). Found %: Ag 28.21, 28.16. $C_{15}H_{13}O_5Ag$. Calculated %: Ag 28.30.

TABLE 4

Comparison of Rates of Rearrangement of Hydroxy- and Methoxybenzils

Expt. No	Benzils compared	Amt. of benzil (in moles)	Solvent and amt. (in ml)	Conc. of KOH (in %)	Boiling time (in min)	Yield of acid or corres. lactone (%)	Recovery of benzil (in %)	Balance (in %)
1	3- Hydroxy-	0.0041	water 30	5	30	89.7	6.4	96.1
	2- Hydroxy-					22.6	72.0	94.6
2*	2- Hydroxy-	0.0041	water 30	15	30	82.3	15.0	97.3
	4- Hydroxy-					34.1	65.6	99.7
3	3,3'- Dihydroxy-	0.0041	water 30	15	30	~ 100	—	~ 100
	2,2'- Dihydroxy-					4.0	95.0	99.0
4*	2,2'- Dihydroxy-	0.0041	water 6	30	240	85.0	10.0	95.0
	4,4'- Dihydroxy-					7.3	92.0	99.3
5	3- Hydroxy-	0.0041	water 30	5	30	90.5	4.3	94.8
	3,3'- Dihydroxy-**					30.7	66.0	96.7
6	3- Methoxy-	0.0050	50% alcohol 35	5	75	84.5	10.0	94.5
	4- Methoxy-					48.8	45.8	94.6
	2- Methoxy-					32.5	64.1	96.6
7	3,3'- Dimethoxy-	0.0045	75% alcohol 35	6	120	92.3	1.7	94.0
	4,4'- Dimethoxy-					40.6	55.0	95.6
	2,2'- Dimethoxy-					18.0	78.3	96.3
8	3- Hydroxy-**	0.0050	50% alcohol 35	5	75	32.8	62.0	94.8
	3- Methoxy-					85.9	9.1	95.0

*Data taken from [1]. Included in this table for convenience in comparison.

**To create more comparable conditions, an equimolecular amount of solid potassium hydroxide (calculated on the basis of one hydroxy group) was added to the solution.

The comparative demethylation of 2,2'-, 3,3'-, 4,4'-, and 2,5-dimethoxybenzils and the synthesis of 3-hydroxy-3'-methoxy- and 5-hydroxy-2-methoxybenzils were carried out under identical conditions. In the first case, 2 g of each of the benzils was dissolved by heating in a mixture of 20 ml of acetic acid and 4 ml of hydrobromic acid (d 1.48). The solutions were boiled simultaneously for 90 min. Ten-percent sodium hydroxide solution was added carefully in 180 ml portions to the reaction mixtures with cooling. The crystalline precipitates of the dimethoxybenzils were filtered off, treated several times with dilute alkali solution until the alkaline filtrate was completely colorless, and then washed with water. The combined alkaline filtrates were acidified until the yellow color disappeared, and the crystalline hydroxymethoxybenzils were filtered off. The 3-hydroxy-3'-methoxy- and 5 hydroxy-2-methoxybenzils which separated out in the form of oils were extracted with ether, the ether solutions were dried with sodium sulfate, and the ether was removed. All of the dimethoxy- and hydroxymethoxybenzils were dried to constant weight.

For the preparative demethylation of large amounts, it is more convenient to pour the reaction mixture into water and after removal of the precipitate to treat the latter with dilute alkali solution. However, larger losses are possible in such treatment The dimethoxybenzils recovered from the reaction usually can be used for a second demethylation without preliminary recrystallization.

Hydroxybenzilic acids and their derivatives. 10 g of hydroxybenzil was dissolved in 50 ml of 20% potassium hydroxide solution and boiled for 1-2 hr. The solution was acidified, extracted with ether, the extract was dried with sodium sulfate, and the ether was removed. Acids (V) and (VIII) crystallized spontaneously or after short periods of trituration. The silver salts and methyl esters of the acids were prepared in the usual way [1].

To methylate the hydroxy acids (VI) and (VIII), 1 g of the acid was dissolved in 10 ml of 10% sodium hydroxide solution and treated, with vigorous stirring and heating for 20-30 min on a water bath, with 2 ml of dimethyl

TABLE 5

Methoxybenzilic Acids

Acids	Melting point		Coloration with conc. H_2SO_4
	our data (solvent for crystallization)	literature data	
2-Methoxy-•	118-119° (benzene + hexane)	100-101° [9] (with $2H_2O$)	Dark red
3-Methoxy-••	Did not crystallize	–	Blue-violet
4-Methoxy-	146-147° (benzene)	147-147.5°[7]	Red-orange
2,2'-Dimethoxy-	159-160° (isopropyl alcohol)	160°[6]	Greenish-blue
3,3'-Dimethoxy-	107-108° (isopropyl alcohol)	105°[8]	Gave no color
4,4'-Dimethoxy-	166-167° (decomp.) (isopropyl alcohol)	165-167°[7]	Purple
2,5-Dimethoxy-•••	120.5-121.5° (benzene)	–	Green, changing rapidly

•Found %: C 70.29, 70.36; H 5.87, 5.76. Equiv. 260.9, 260.0. $C_{15}H_{14}O_4$. Calculated %: C 69.81; H 5.46. Equiv 258.3.

••Could not be obtained in crystalline form. Ag salt. Found %: C 49.69, 49.13; H 3.63, 3.89; Ag 29.88, 29.83. $C_{15}H_{13}O_4Ag$. Calculated %: C 49.37; H 3.59; Ag 29.55.

•••Found %: C 67.03, 67.11; H 5.58, 5.88. Equiv. 290.7, 290.2. $C_{16}H_{16}O_5$. Calculated %: C 66.65; H 5.58. Equiv. 288.3.

sulfate. Then an excess of concentrated alkali solution was added and the mixture was stirred, with heating, for another 20-30 min. After this, the mixture was diluted with water, extracted with ether to remove neutral contaminants, acidified, and again extracted with ether. The acids were recrystallized and identified.

Methoxybenzilic acids. The methoxybenzils (5 g) were boiled for 10 min in a solution of 2.5 g of KOH in 13 ml of n-butyl alcohol [6]. The solution was diluted with ether and extracted 3 times with water. The aqueous extracts were washed with ether and acidified. The crystalline acids were filtered off, and those which separated out in the form of oils were extracted with ether. If the product did not crystalline, it was subjected to additional treatment. The acid was dissolved in 5% Na_2CO_3 solution and the solution was extracted with ether and acidified.

Experiments to evaluate the relative rates of rearrangement. In each experiment (Table 4) equimolecular amounts of the benzils to be compared were boiled simultaneously in various volumes of potassium hydroxide solution of the same concentration. Treatment of the reaction mixtures in Expts. No. 1, 3, and 5 was carried out in the same way as in previous work [1]. In Expts. No. 6-8 the solutions after boiling were diluted with water. The unreacted crystalline benzils were filtered off and the ones that separated out in the form of oils were extracted with ether.• The aqueous solutions were acidified and treated in the same way. The ether solutions were dried with sodium sulfate and the ether was removed. All of the products were dried to constant weight.

SUMMARY

1. The rearrangement of four hydroxybenzils containing hydroxyl groups in the meta position has been carried out.

2. It has been shown that for the hydroxybenzils the rate of rearrangement decreases in the series meta > ortho > para, but for the methoxybenzils it decreases in the series meta > para > ortho.

•In Expt. No. 8 the solution containing the hydroxy derivative was saturated in advance with carbon dioxide.

3. It has been established that meta-methoxy groups in methoxybenzils are demethylated with hydrobromic acid with greater speed than the ortho- and para-methoxy groups.

4. A number of new hydroxy- and methoxybenzils, benzilic acids, and derivatives of them have been prepared and characterized.

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ARYLAMIDES OF ALIPHATIC AMINO ACIDS

II. ARYLAMIDES OF GLYCINE AND GLYCYLGLYCINE

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Translated from Zhurnal Obshchei Khimii, Vol. 130. No. 6, pp. 1848-1855,
June, 1960
Original article submitted June 9, 1959

In the synthesis of the arylamides of glycine and glycylglycine we have employed a method of protecting the amino group with a triphenylmethyl (trityl) radical.•

The triphenylmethyl derivatives of the amino acids have been described in the literature [1] and have recently been widely used by French scientists in their work with amino acids and peptides. Advantages of this method of protecting the amino group are the relative stability of the trityl group toward alkalies and the ease with which it is split off in acid medium.

We prepared N-tritylglycine according to information in the literature [2] from the ethyl or methyl ester of glycine by the action of triphenylchloromethane and subsequent saponification of the ester group in the esters of N-tritylglycine.

The starting materials for the preparation of N-tritylglycylglycine were N-tritylglycine and the ethyl ester of glycine; the ester of N-tritylglycylglycine obtained from these compounds was saponified to N-tritylglycylglycine. The reaction between N-tritylglycine and the ethyl ester of glycine was carried out by two methods: by the reaction of a mixed anhydride of N-tritylglycine and the ethyl ester of glycine as described in [2], with slight modifications, and by the direct reaction of N-tritylglycine with the ethyl ester of glycine in the presence of dicyclohexylcarbodiimide; the latter method had been recommended in its time for the preparation of compounds with a peptide linkage [3] and had not yet been used for the preparation of N-tritylglycylglycine.

$$(C_6H_5)_3CNHCH_2COOH + H_2NCH_2COOC_2H_5 \xrightarrow{C_6H_{11}N=C=NC_6H_{11}} (C_6H_5)_3CNHCH_2CONHCH_2COOC_2H_5 + C_6H_{11}NHCONHC_6H_{11}$$

The latter method gave better results, with the yield of the ester of N-tritylglycylglycine amounting to 90%, while the yield when the reaction was carried out by means of the mixed anhydride did not exceed 86%. Apparently the mixed anhydride of N-tritylglycine did not react completely, since when the reaction products were treated with methyl alcohol we obtained along with other compounds, the methyl ester of N-tritylglycine, which in this case could be formed only from the mixed anhydride of N-tritylglycine. We observed similar effects also in other cases where the method employing the mixed anhydride was used for the formation of a peptide linkage.

When we repeated experiments saponifying the ester group of the ethyl ester of N-tritylglycine, we did not obtain a compound with a melting point exactly coinciding with that indicated in the literature; furthermore, the data in the literature on the melting point of N-tritylglycine are inconsistent, and we therefore needed to investigate

•In our previous communication [Zhur. Obshchei Khim. 29, 3391 (1959)] the amino group in the amino acids was protected with a phthalyl group.

this reaction is more detail. We carried out experiments on the saponification under various conditions; we varied the reaction temperature, the duration of the heating period, the amount of alkali, etc.; in this way we found the optimum conditions, under which N-tritylglycine was obtained in 97% yield. The least deviation from these conditions caused a decrease in the yield and a change in the melting point of the compound that was separated.

The difference in the results is related to the fact that partial splitting off of the trityl group takes place along with the saponification of the ester group; in many experiments we isolated triphenylcarbinol and glycine, in addition to N-tritylglycine. The quantitative proportions of the compounds that were formed depended on the experimental conditions. There are indications that the trityl group can be split off also under the influence of the lower alcohols [4]. We also should take notice of the fact that N-tritylglycine gradually decomposes on heating, and therefore the method of determining its melting point (apparatus, rate of raising the temperature, etc.) acquires great importance.

When the ethyl ester of N-tritylglycylglycine was saponified, we observed similar phenomena; however, in this compound the trityl group is split off more easily than in N-tritylglycine; even a slight increase in the amount of alkali and the duration of heating caused a lowering of the yield of N-tritylglycylglycine from 95 to 60%.

For the preparation of the arylamides of glycine (I and II) the starting material was N-tritylglycine, which was combined with the aromatic amines: β-naphthylamine and N,N-di(β-chloroethyl)-p-phenylenediamine "A",* $H_2NC_6H_4N(CH_2CH_2Cl)_2$; for this purpose we employed both the method using the mixed anhydrides and the direct reaction of N-tritylglycine and the aromatic amine in the presence of dicyclohexylcarbodiimide.

In the N-tritylglycylamides obtained in this way the trityl group was easily split off by means of 75% acetic acid.

$$NH_2CH_2CONHR \begin{cases} (I)\ R = \beta\text{-}C_{10}H_7. \\ (II)\ R = C_6H_4N(CH_2CH_2Cl)_2. \end{cases}$$

Different methods were tried for the preparation of the arylamide of N-tritylglycylglycine (III). In variations "a" and "b" (see diagram) the acylating agent, as in the cases described above, was N-tritylglycine as such (a) or in the form of the mixed anhydride (b) and the compound acylated was 1-N'-glycyl-4-N", N"-di(β-chloroethyl)-phenylenediamine (II). Both variations gave positive results with the production of the dipeptide (III). In variation "c" the reactants were N-tritylglycylglycine and diamine "A". In this case positive results were achieved only by the method of [3]. Experiments on carrying out the reaction with the mixed anhydride of N-tritylglycylglycine gave negative results.

Scheme

$$\text{a, b}\ \{(C_6H_5)_3CNHCH_2COOH\ (I) + NH_2CH_2CONHC_6H_4N(CH_2CH_2Cl)_2\ (II) \xrightarrow{\text{a } C_6H_{11}N{=}C{=}NC_6H_{11}} \xrightarrow{\text{b } ClCOOCH_3}$$

$$(C_6H_5)_3CNHCH_2CONHCH_2CONHC_6H_4N(CH_2CH_2Cl)_2\ (III)$$

$$\text{c}\ \{(C_6H_5)_3CNHCH_2CONHCH_2COOH + NH_2C_6H_4N(CH_2CH_2Cl)_2 \xrightarrow{C_6H_{11}N{=}C{=}NC_6H_{11}} \xrightarrow{75\%\ CH_3COOH}$$

$$NH_2CH_2CONHCH_2CONHC_6H_4N(CH_2CH_2Cl)_2\ (IV)$$

Compound (IV) 1-N'-glycylglycyl-4-N", N"-di(β-chloroethyl)phenylenediamine was easily obtained from compound (III) by hydrolysis of the trityl group with 75% acetic acid.

*Compound "A" was prepared as described in [5] with the sole difference that the hydrochloride of this diamine was purified by chromatography.

EXPERIMENTAL

The ethyl and methyl esters of N-tritylglycine were prepared according to information in the literature as indicated above from the corresponding esters of glycine (hydrochlorides) and triphenylchloromethane in chloroform solution and in the presence of triethylamine. The methyl ester of N-tritylglycine after recrystallization from anhydrous methyl alcohol melted at 103-104°. After repeated recrystallization, a sample for analysis melted at 106-106.5° (according to the literature [2] m.p. 106-107°). The ethyl ester of N-tritylglycine, recrystallized from petroleum ether, melted at 112.5-113.5°.

1. Ethyl ester of N-tritylglycylglycine a) To a solution of 5.0 g of N-tritylglycine in 60 ml of anhydrous chloroform containing 3.2 g of triethylamine was added 1.72 ml of methyl chloroformate at −10° and with vigorous stirring. After the mixture had been stirred for 1.5 hr at the same temperature, a solution of 2.19 g of the hydrochloride of the ethyl ester of glycine in 40 ml of chloroform containing 3.2 ml of triethylamine was added and the mixture was stirred for 1 hr at room temperature. Then the chloroform solution was washed with water and dried. After the chloroform had been distilled off and the remaining crystalline material had been recrystallized from benzene, 5.1 g of the ethyl ester of N-tritylglycylglycine was obtained with m.p. 161-162° [1, 2]. By evaporation of the mother liquor and recrystallization of the residue first from benzene and then twice from anhydrous alcohol, 0.44 g of the ethyl ester of N-tritylglycylglycine was obtained with m.p. 159-160° (total yield 5.45 g, 86%) and 0.54 g of the ethyl ester of N-tritylglycine with m.p. 109-110°; after recrystallization from a mixture of benzene and petroleum ether, m.p. 112-113°.

b) To a solution of the ethyl ester of glycine (b.p. 63° at 30 mm) in 5 ml of anhydrous chloroform was added a solution of 2.5 g of N,N'-dicyclohexylcarbodiimide in 5 ml of anhydrous chloroform. The chloroform solution was cooled to 0° and a solution of 3.17 g of N-tritylglycine in 30 ml of anhydrous chloroform was added to it with vigorous stirring. The reaction mixture was left to stand overnight, the N,N'-dicyclohexylurea that had precipitated was filtered off, and the chloroform solution was washed with 1 N hydrochloric acid, ammonia, and water and was dried with sodium sulfate. The chloroform was distilled off and the white crystalline compound was recrystallized from benzene. 3.2 g of the ethyl ester of N-tritylglycylglycine was obtained with m.p. 161-162°. By evaporation of the mother liquor another 0.76 g was obtained with m.p. 159-160°. The total yield of the ethyl ester of N-tritylglycylglycine was 3.98 g (99%).

2. N-Tritylglycine. To a boiling solution of 3.2 g of potassium hydroxide in 20 ml of anhydrous methyl alcohol was added 10.1 g of the ethyl ester of N-tritylglycine. After 2 min boiling, 30 ml of water was added to the solution that was obtained, the methyl alcohol was distilled off, and the remaining alkaline solution was acidified with acetic acid until it was acid to litmus. The white amorphous material that precipitated was filtered off. 9.56 g (97%) of material was obtained, which shrank and was converted to a caramel-like mass at 156-158°; the material melted completely at 175-180°. For analysis the N-tritylglycine was recrystallized twice from anhydrous methyl alcohol and dried in a vacuum desiccator over phosphorus pentoxide. M.p. 176-178° (on a Kofler block) [1, 2].

Found %: C 79.35; H 6.04; N 4.51. $C_{21}H_{19}O_2N$. Calculated %: C 79.46; H 6.03; N 4.41.

N-tritylglycine was prepared by the same method from the methyl ester of N-tritylglycine.

3. N-Tritylglycylglycine. To a boiling solution of 0.85 g of potassium hydroxide in 12 ml of methyl alcohol was added 2.13 g of the ethyl ester of N-tritylglycylglycine. After 3 min boiling, 10 ml of water was added to the solution that was obtained, the methyl alcohol was distilled off, and the alkaline solution was acidified to litmus with acetic acid. The amorphous material that precipitated was filtered off and recrystallized from anhydrous methyl alcohol and dried over phosphorus pentoxide. 1.42 g of N-tritylglycylglycine was obtained with m.p. 175-180° (in an apparatus with sulfuric acid; the capillary was inserted in the cold apparatus). When the melting point of this compound was determined on a Kofler block (compound inserted in the apparatus at 160-165°) the m.p. was 179-180°. By evaporation of the mother liquor another 0.33 g was obtained with m.p. 175-180°. The total yield of N-tritylglycylglycine was 1.75 g (89%).

Found %: C 73.95; H 6.25; N 7.45. $C_{23}H_{22}O_3N_2$. Calculated %: C 73.76; H 5.92; N 7.48.

4. 1-N'-(N-Tritylglycyl)-4-N", N"-di(β-chloroethyl)phenylenediamine. The starting N,N-di(β-chloroethyl)-p-phenylenediamine was prepared according to directions in the literature by nitrosation of N-di(chloroethyl)aniline and subsequent reduction with stannous chloride of the 1,4-nitroso-N,N-di(β-chloroethyl)aniline.

The diamine obtained was purified in another way than that described in the literature [5], namely: the reaction product, after reduction, was filtered off, washed with hydrochloric acid and with ether and dried, after which it was dissolved in methyl alcohol and the alcoholic solution was passed through a column with aluminum oxide. the eluate was evaporated to a volume of 50-60 ml and the hydrochloride of N,N -di(β-chloroethyl)-p-phenylenediamine was precipitated from the alcoholic solution with anhydrous ether. Yield 78%. M. p. 268-270° (decomp.). A capillary with the compound was immersed in an apparatus that had been heated to 220°; the rate of heating was 2° per min. According to data in the literature [5], m.p. 250-260° (decomp.).

a) To a solution of 3.73 g of N-tritylglycine in 30 ml of anhydrous chloroform containing 2.05 ml of triethylamine was added 1.03 ml of methyl chloroformate at −10° with vigorous stirring. After the mixture had been stirred at the same temperature for 1.5 hr, a solution of 3.16 g of the hydrochloride of N,N-di(β-chloroethyl)-p-phenylenediamine in 40 ml of chloroform containing 1.68 ml of triethylamine was added. When the addition of the chloroform solution had been completed, stirring was continued for 1 hr more at room temperature and then the reaction mixture was repeatedly washed with water and dried with magnesium sulfate. The chloroform was distilled off and the remaining oily material was triturated while being cooled, with 8 ml of anhydrous alcohol. The material that precipitated was filtered off and recrystallized from anhydrous benzene. 3.92 g of 1-N'-(N-tritylglycyl)-4-N", N"-di(β-chloroethyl)phenylenediamine was obtained with m.p. 174-175°.

By evaporation of the mother liquor another 1.01 g of material was obtained with m.p. 170-172°. Total yield 4.03 g (66.5%).

For analysis the compound was recrystallized twice from anhydrous benzene. It was a white amorphous material with m.p. 177-177.5° (when the capillary with the compound was inserted in an apparatus heated to 100°; the rate of melting was 2° per minute). insoluble in water, difficultly soluble in alcohol, soluble in chloroform and benzene.

Found %: C 70.10; H 5.99; N 7.70; Cl 13.41. $C_{31}H_{31}ON_3Cl_2$. Calculated %: C 69.93; H 5.86; N 7.89; Cl 13.31.

b) To a suspension of 3.17 g of N-tritylglycine in 40 ml of anhydrous chloroform were added 2.06 g of N,N'-dicyclohexylcarbodiimide in 10 ml of anhydrous chloroform and a solution of N,N-di(β-chloroethyl)-p-phenylenediamine in 30 ml of chloroform. [The N,N-di(β-chloroethyl)-p-phenylenediamine was prepared from 2.27 g of its hydrochloride by treatment of the latter in the cold with a saturated solution of sodium carbonate and extraction of the base with chloroform.] The reaction mixture was stirred at room temperature for 5 hr, then left overnight. The N,N'-dicyclohexylurea (2.2 g) was filtered off from the chloroform solution and part of the chloroform was distilled off. The additional quantity of N,N'-dicyclohexylurea that precipitated (0.5 g) was filtered off (in all, 2.7 g of N,N'-dicyclohexylurea was obtained). Then the chloroform was completely distilled off from the filtrate and the remaining amorphous material was recrystallized from benzene. 4.1 g of 1-N'-(N-tritylglycyl)-4-N", N"-di(β-chloroethyl)phenylenediamine was obtained with m.p. 171-172° (yield 77%). A mixed sample with the compound obtained by the first method melted at 171-172°.

5. 1-N'-Glycyl-4-N", N"-di(β-chloroethyl)phenylenediamine (hydrochloride). To 20 ml of a 75% aqueous solution of acetic acid was added 3.78 g of 1-N'-(N-tritylglycyl)-4-N", N"-di(β-chloroethyl)phenylenediamine, and the mixture was heated on a boiling water bath for 5 min. The solution that was obtained was cooled to −10° and the triphenylcarbinol that precipitated was filtered off. The mother liquor was evaporated in vacuum to dryness at a temperature not higher than 50°. The oily material that was obtained was dissolved in anhydrous alcohol; to the solution was added alcohol saturated with hydrogen chloride, the alcoholic solution was evaporated to a small volume and cooled. The crystalline material that precipitated was recrystallized from anhydrous methyl alcohol. 1.51 g of the hydrochloride of 1-N'-glycyl-4-N", N"-di(β-chloroethyl)phenylenediamine was obtained with m.p. 242-243° (decomp.). From the mother liquor another 0.61 g of the compound was obtained with m.p. 241-242°. Total yield 2.11 g.

For analysis the compound obtained was recrystallized from methyl alcohol in the form of needles with a slight rose color, m.p. 245° (decomp.), soluble in water and alcohol.

Found %: C 43.88; H 5.52; Cl' 11.02. $C_{12}H_{17}ON_3Cl_2 \cdot HCl$. Calculated %: C 44.12; H 5.55; Cl 10.85.

6. N-Tritylglycyl-β-naphthylamine. The reaction was carried out in the same way as in Expt. 4a. We used a solution of 5.88 g of N-tritylglycine in 60 ml of anhydrous chloroform containing 3.25 ml of triethylamine,

1.63 ml of methyl chloroformate, and 2.68 g of β-naphthylamine in 30 ml of chloroform. After the reaction had been carried out, the reaction product treated in the way previously described, and the chloroform distilled off, an oily material was obtained, which crystallized when triturated with anhydrous alcohol. 4.95 g of N-tritylglycyl-β-naphthylamine was obtained with m.p. 196-197° (from ethyl acetate). From the mother liquor we obtained another 0.71 g with m.p. 194-196°. Total yield 5.66 g (69.1%).

For analysis the N-tritylglycyl-β-naphthylamine was recrystallized twice from ethyl acetate and colorless crystals were obtained with m.p. 199.5-200°, insoluble in water, poorly soluble in alcohol, soluble in chloroform and ethyl acetate.

Found %: C 83.92; H 5.99; N 6.45. $C_{31}H_{26}ON_2$. Calculated %: C 84.13; H 5.92; N 6.33.

7. Glycyl-β-naphthylamine (hydrochloride). The reaction was carried out in the same way as in Expt.5. We used 15 ml of 75% aqueous acetic acid solution and 2.21 g of N-tritylglycyl-β-naphthylamine. After the triphenylcarbinol had been removed, the mother liquor was evaporated in vacuum at a temperature not higher than 50°. The oily material was dissolved in anhydrous alcohol, and alcohol saturated with hydrogen chloride was added to the solution; the alcoholic solution was evaporated to a small volume and cooled. The crystalline material that precipitated was filtered off and recrystallized from anhydrous alcohol. 0.86 g of the hydrochloride of glycyl-β-naphthylamine was obtained with m.p. 225-227° (decomp.). From the mother liquor another 0.05 g of the compound was obtained with m.p. 223-225° (decomp.). Total yield 0.91 g (77.12%).

For analysis the hydrochloride of glycyl-β-naphthylamine was recrystallized once more from alcohol as colorless crystals, m.p. 226-227° (decomp.), soluble in water and alcohol.

Found %: C 60.62; H 5.41; N 11.80; Cl' 15.28. $C_{12}H_{12}ON_2 \cdot HCl$. Calculated %: C 60.88; H 5.53; N 11.83; Cl' 14.98.

8. 1-N'-(N-Tritylglycylglycyl)-4-N", N"-di(β-chloroethyl)phenylenediamine.

a) The reaction was carried out in the same way as in Expt. 4a. We used a solution of 0.33 g of N-tritylglycine in 5 ml of anhydrous chloroform containing 0.2 ml of triethylamine and 0.1 ml of methyl chloroformate. After 1.5 hr stirring at −10° a solution of 0.34 g of the hydrochloride of 1-N'-glycyl-4-N", N"-di(β-chloroethyl)-phenylenediamine in 20 ml of anhydrous chloroform containing 1 ml of triethylamine was added. The reaction mixture was stirred for 1 hr at room temperature, then the chloroform solution was washed with water and dried with magnesium sulfate. After the chloroform had been distilled off, a crystalline material was obtained which was washed with anhydrous alcohol, then dissolved in ethyl acetate. The solution was evaporated to a small volume and cooled. The crystalline material that precipitated was filtered off. 0.35 g (55.5%) of 1-N'-(N-tritylglycylglycyl)-4-N", N"-di(β-chloroethyl)phenylenediamine was obtained with m.p. 205-206° (decomp.) (the capillary was inserted in the apparatus which was heated to 200°; the rate of melting was 2° per minute).

For analysis the compound was dissolved in chloroform, part of the chloroform was distilled off, the solution was cooled, and the tritylglycylglycyldi(β-chloroethyl)-p-phenylenediamine that precipitated was filtered off; a colorless amorphous material was obtained with m.p. 205-206° (decomp.), soluble in water, chloroform, and ethyl acetate, difficultly soluble in anhydrous alcohol.

Found %: C 66.92; H 5.81; N 9.25. $C_{33}H_{34}O_2N_4Cl_2$. Calculated %: C 67.22; H 5.81; N 9.50.

b) To a suspension of 1.16 g of the hydrochloride of 1-N'-glycyl-4-N", N"-di(β-chloroethyl)phenylenediamine in 20 ml of chloroform was added 0.5 ml of triethylamine, then after 15 min stirring at room temperature 0.9 g of N,N'-dicyclohexylcarbodiimide and 1.13 g of N-tritylglycine were added. The mixture was stirred at room temperature for 4 hr, then left overnight. The N,N'-dicyclohexylurea that had precipitated was filtered off and the chloroform was distilled off from the filtrate. The white amorphous material obtained was washed 3 times with alcohol. 1.79 g (85.2%) of 1-N'-(N-tritylglycylglycyl)-4-N", N"-di(β-chloroethyl)phenylenediamine was obtained with m.p. 204-205° (decomp.) (capillary inserted in apparatus heated to 200°; rate of melting 2° per minute). A mixed sample with the compound obtained by the first method melted at 204-205° (decomp.).

c) To a suspension of 0.87 g of N-tritylglycylglycine in 10 ml of anhydrous chloroform was added a solution of 0.61 g of N,N'-dicyclohexylcarbodiimide in 8 ml of chloroform. Then, while the mixture was stirred a chloroform solution of N,N-di(β-chloroethyl)-p-phenylenediamine was added [prepared from 0.63 g of the

hydrochloride of N,N-di(β-chloroethyl)-p-phenylenediamine by the addition of a saturated solution of sodium carbonate and extraction of the base with chloroform]. The reaction mixture was stirred for 6 hr at room temperature and left to stand overnight. The chloroform solution was evaporated to $\frac{1}{3}$ its volume and the N,N'-dicyclohexylurea was filtered off. From the filtrate the chloroform was completely distilled off. The remaining material was washed with anhydrous alcohol and with benzene. 1.05 g (76.2%) of 1-N'-(N-tritylglycylglycyl)-4-N", N"-di(β-chloroethyl)phenylenediamine was obtained with m.p. 204-205° (decomp.) (capillary was inserted in apparatus heated to 200°). A mixed sample with 1-N'-(N-tritylglycylglycyl)-4-N", N"-di(β-chloroethyl)-phenylenediamine prepared by variations "a" and "b" melted at 204-205° (decomp.).

9. 1-N'-Glycylglycyl-4-N", N"-di(β-chloroethyl)phenylenediamine (hydrochloride). To 10 ml of an aqueous solution of acetic acid was added 1.18 g of 1-N'-(N-tritylglycylglycyl)-4-N", N"-di(β-chloroethyl)-phenylenediamine, and the mixture was heated on a boiling water bath for 5 min. The solution obtained was cooled to −10° and the triphenylcarbinol that precipitated was filtered off. The mother liquor was evaporated in vacuum to dryness at a temperature not higher than 50°. To the oily material that was obtained was added 5 ml of alcohol saturated with hydrogen chloride. The alcoholic solution was evaporated and the white amorphous material that precipitated was washed with alcohol and recrystallized from aqueous methyl alcohol (1 : 1). 0.68 g (89.3%) of the hydrochloride of 1-N'-glycylglycyl-4-N", N"-di(β-chloroethyl)phenylenediamine was obtained with m.p. 272-274° (decomp.). For analysis the compound was recrystallized once more from aqueous methyl alcohol. Colorless crystals were obtained in the form of needles, m.p. 276-278° (decomp.), soluble in hot water.

Found %: C 44.01; H 5.41; N 14.72. $C_{14}H_{20}O_2N_4Cl_2 \cdot HCl$. Calculated %: C 43.82; H 5.52; N 14.60.

SUMMARY

1. A method had been described for the preparation of the ethyl ester of N-tritylglycylglycine from N-tritylglycine and the ethyl ester of glycine in the presence of dicyclohexylcarbodiimide.

2. The conditions for the saponification of the ethyl esters of N-tritylglycine and N-tritylglycylglycine have been defined more precisely.

3. Glycyl-β-naphthylamine; 1-N'-glycyl-4-N", N"-di(β-chloroethyl)phenylenediamine; and 1-N'-glycylglycyl-4-N", N"-di(β-chloroethyl)phenylenediamine have been prepared.

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CONDENSED POLYMETHYLENE DERIVATIVES OF HETEROCYCLIC COMPOUNDS ON THE BASIS OF LACTAMS

II. ON THE CAPACITY FOR REARRANGEMENT OF 2-PHENYL-4 (2'-HOMOPIPERIDYLEN)OXAZOLONE-5 TO 2-PHENYL-1,5-PENTAMETHYLENIMIDAZOLE-4-CARBOXYLIC ACID AND ITS METHYL ESTER

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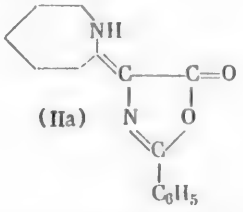
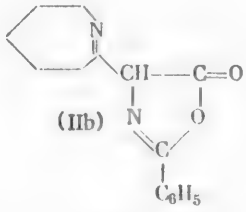
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1855-1860, June, 1960
Original article submitted June 10, 1959

In our preceding article [1] the possibility of synthesizing polymethylene derivatives of heterocyclic compounds and, in particular, polymethylenimidazoles from O-methylcaprolactim (I) was indicated.

The ability of O-methylcaprolactim (I) to condense with compounds having an active methylene group [2] made it possible for us to prepare 2-phenyl-4-(2'-homopiperidylen)oxazolone-5 (IIa) through the reaction of O-methylcaprolactim (I) with 2-phenyloxazolone-5 [3]. Of the two possible structural formulas for the product in this case (IIa, IIb), structure IIa must be considered more correct on the basis of the presence of an absorption band in the IR spectrum* at 3271 cm^{-1}, which is characteristic of the NH bond, and also the UV spectrum (λ_{max} 238 mμ, ε 3,829; λ_{max} 294 mμ, ε 3,770; λ_{max} 352 mμ, ε 4,062), which indicates the presence of conjugated double bonds. Compound (IIa) was also synthesized through the reaction of (I) with hippuric acid in the presence of acetic anhydride.



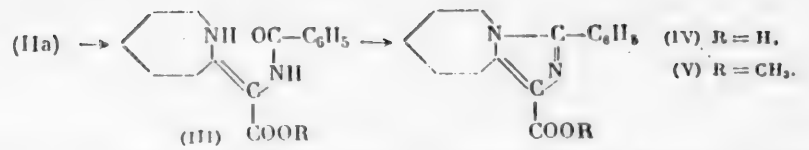
(IIa)



(IIb)

On alkaline hydrolysis of (IIa) by methanolic potassium hydroxide solution, instead of the expected formation of the corresponding α-amino- or α-benzoylaminoacrylic acids usually formed on cleavage of oxazolones-5, there was obtained an acid of the same composition as (IIa), which was easily decarboxylated on heating. When the hydrolysis was carried out under milder conditions, not only the new acid, but also its methyl ester, was obtained. We advanced the hypothesis of intramolecular conversion of 2-phenyl-4-(2'-homopiperidylen)oxazolone-5 to 2-phenyl-1,5-pentamethylenimidazole-4-carboxylic acid (IV) through α-benzoylamino-β-(2'-homopiperidylene)acrylic acid (III).

*The spectral study of our compounds was carried out by Yu. N. Sheinker and E. M. Pereslena, to whom we extend out thanks.



This conversion is supported by the IR absorption spectrum of (V), which did not contain the above-mentioned 3271 cm^{-1} absorption band characteristic of the NH group, but did have the 1699 cm^{-1} absorption band due to the ester grouping. The simple ester grouping is characterized by an absorption band at 1735 cm^{-1} [4]. The shift of this band toward shorter wavelengths indicates the presence in ester (V) of a conjugated system of the double bond in the ring with the carbomethoxyl double bond (> C = O– –C = O).

The formation of ester (V) explains the appearance of such properties as the easy decarboxylation of acid (IV), which gives an 88% yield of 2-phenyl-1,5-pentamethylenimidazole, and the fact that (V) is almost wholly lacking in basic properties.

In the literature a similar kind of rearrangement is described where 2-phenyl-4-(2'-carbomethoxybenzyliden)oxazolone-5 is converted to isocarbostyril on heating with methanolic potassium hydroxide solution [5].

On the other hand, when the hydrochloride of (IIa) was briefly hydrolyzed in methanol, methyl α-benzoylamino-β-(2'-homopiperidylene)acrylate (III) was obtained as the hydrochloride; on further heating with methanolic HCl, the latter gave (V). Moreover, alcoholysis of (IIa) in methanol in the presence of HCl gave a mixture of (III) and (V), which was resolved. All these conversions conclusively prove to us that the scheme of conversion of oxazolone (IIa) to imidazole derivatives (IV-V), indicated above, is correct. We wished to confirm this scheme further by the countersynthesis of 1,5-pentamethylene-2-phenylimidazole. For this, lactim (I) was condensed with nitromethane to form α-(2'-homopiperidylene)nitromethane (VI), for the purpose of reducing the latter to an aminomethyl derivative and then acylating, and closing the imidazole ring. In the reduction of (VI), however, difficulties were encountered which have not yet been overcome. The investigation is continuing.

EXPERIMENTAL

2-Phenyl-4-(2'-homopiperidylen)oxazolone-5 (IIa). a) A mixture of 20 g of O-methylcaprolactim and 9 g of 2 phenyloxazolone-5 was heated for 1 hr at 110-115°; in this case the solid matter completely dissolved, and the reaction mass was concentrated by evaporation in vacuo. There was obtained 12.6 g (88%) of 2-phenyl-4-(2'-homopiperidylen)oxazolone-5, m.p. 120-122°. After crystallization (1 : 30) from a 1 : 4 benzene–ether mixture it consisted of long tablets with m.p. 129.5-131.5°. The substance was difficultly soluble in water, dilute acids, and alkalis, soluble in the cold in acetone, chloroform, and benzene, and soluble on heating in alcohol.

Found %: C 70.73; H 6.27; N 11.46. $C_{15}H_{16}O_2N_2$. Calculated %: C 70.32; H 6.25; N 10.94.

b) A mixture of 42 g of hippuric acid, 85 ml of acetic anhydride, and 60 g of O-methylcaprolactim was heated for 1 hr at 65-70°; on cooling, the reaction mass was filtered and the precipitate washed with ether. The yield of 2 phenyl-4-(2'-homopiperidylen)oxazolone-5 was 28.7 g, m.p. 126-129°. On cooling (–7°, 2 days), another 5.3 g of the substance (m.p. 129-131°) separated from the mother liquor.

2-Phenyl-4-(2'-homopiperidylen)oxazolone-5 hydrochloride. A current of dry hydrogen chloride was passed through a suspension of 10.24 g of 2-phenyl-4-(2'-homopiperidylen)oxazolone-5 in 100 ml of 99.9% methanol at –10° for 3 hr; in this case the solid phase turned yellow; the latter was filtered out, and washed with 10 ml of methanol. The yield of 2-phenyl-4-(2'-homopiperidylen)oxazolone-5 hydrochloride was 11.45 g (97.86%). The substance was yellow (prisms, coalescing in nodules), slightly soluble in water and most organic solvents. For analysis 0.2 g was crystallized from a mixture of 10 ml of anhydrous benzene and 2.5 ml of anhydrous chloroform; m.p. 191-193°.

Found %: Cl 12.38, 12.45. $C_{15}H_{16}O_2N_2 \cdot HCl$. Calculated %: Cl 12.49.

On prolonged trituration with 5% sodium bicarbonate solution the original base (IIa), m.p. 122-126°, was recovered.

Methyl α-benzoylamino-β-(2'-homopiperidylene)acrylate hydrochloride. A mixture of 10 g of 2-phenyl 4-(2'-homopiperidylen)oxazolone-5 hydrochloride, 100 ml of 99.5% methanol, and 0.5 ml of water was boiled for 30 min and the resulting solution evaporated to ¼; in this case 8.25 g (83.7%) of methyl α-benzoylamino-β-(2'-homopiperidylene)acrylate hydrochloride, m.p. 156-158°, separated in the form of colorless prisms, after crystallization of 0.5 g of the substance from 5 ml of methanol, m.p. 158-160° (with gas evolution). The substance was slightly soluble in water and most organic solvents.

Found %: N 8.52; Cl 11.08. $C_{16}H_{20}O_3N_2 \cdot HCl$. Calculated %: N 8.62; Cl 11.26.

Methyl 2-phenyl-1,5-pentamethylenimidazole-4-carboxylate (V). One g of methyl α-benzoylamino-β-(2'-homopiperidylene)acrylate hydrochloride was boiled for 5 hr with 20 ml of a 15% solution of hydrogen chloride in methanol, the reaction mass was evaporated, and the residual oil was dissolved in the cold in 4 ml of water, the solution brought to pH 8 with saturated soda solution, and the resulting precipitate filtered out, and washed with 5 ml of cold water. There was obtained 0.55 g (67.07%) of methyl 2-phenyl-1,5-pentamethylenimidazole-4-carboxylate, m.p. 161-163°. After crystallization of 0.5 g from a mixture of 15 ml of ether and 10 ml of benzene, m.p. 164.5-165.5° (tablets). The substance was soluble in the cold in chloroform and on heating, in acetone, benzene, and methanol; it was slightly soluble in ether, ethyl acetate, and water.

Found %: C 71.00, 71.16; H 6.57, 6.72; N 10.54. $C_{16}H_{18}O_2N_2$. Calculated %: C 71.11; H 6.66; N 10.38.

Alcoholysis of 2-phenyl-4-(2'-homopiperidylen)oxazolone-5 in the presence of hydrogen chloride. Twelve g of 2-phenyl-4-(2'-homopiperidylen)oxazolone-5 was boiled for 2 hr in 150 ml of a 10% solution of hydrogen chloride in methanol; in the course of boiling the solid phase first turned yellow and then dissolved to form a yellow solution; this was evaporated, after which the residual oil crystallized after several washings with ether. There was obtained 3.75 g (24.7%) of methyl α-benzoylamino-β-(2'-homopiperidylene)acrylate hydrochloride, m.p. 158-160° (with gas evolution). The washings were evaporated, and the residual oil was dissolved in 10 ml of water and brought to pH 8 by treatment in the cold with 5% soda solution; in this case 3.6 g (28.46%) of methyl 2-phenyl-1,5-pentamethylenimidazole-4-carboxylate, m.p. 159-161°, separated out.

2-Phenyl-1,5-pentamethylenimidazole-4-carboxylic acid (IV). a) To 30 ml of a 10% solution of potassium hydroxide in methanol, 6 g of 2-phenyl-4-(2'-homopiperidylen)oxazolone-5 was added. The mixture was boiled for 5 hr. On cooling, the resulting potash precipitate was filtered out, the filtrate evaporated, the residue dissolved in 30 ml of water, and the solution acidified to a pH of about 6.5; in this case an oil separated, which was extracted with chloroform, the extract dried with anhydrous Na_2SO_4 and distilled, and the residue triturated with ether. There was obtained 4.05 g (67.5%) of 2-phenyl-1,5-pentamethylenimidazole-4-carboxylic acid, m.p. 162-164°; after crystallization of 0.5 g from 12 ml of 99.9% methanol and 20 ml of ether, m.p. 164-165° (prisms, coalescing in nodules). The substance was very slightly soluble in ether and more soluble in water, benzene, and ethyl acetate; it was soluble in the cold in acetone, methanol, and chloroform; it vigorously evolved gas when dissolved in sodium bicarbonate solution.

Found %: N 11.16, 11.00. $C_{15}H_{16}O_2N_2$. Calculated %: N 10.94.

b) A 16.8 g quantity of 2-phenyl-4-(2'-homopiperidylen)oxazolone-5 was boiled with 50 ml of a 10% solution of potassium hydroxide in methanol for 30 min, the methanol distilled off, and the residue dissolved in 20 ml of water and filtered; 7.5 g (42.37%) of methyl 2-phenyl-1,5-pentamethylenimidazole-4-carboxylate, m.p. 160-162°, was obtained, whereas the filtrate, acidified in the cold with 10% hydrochloric acid to pH 6.5 and treated as in the preceding, gave 5 g (29.76%) of 2-phenyl-1,5-pentamethylenimidazole-4-carboxylic acid, m.p. 161-163°.

2-Phenyl-1,5-pentamethylenimidazole. Five g of 2-phenyl-1,5-pentamethylenimidazole-4-carboxylic acid was heated for 3 hr in a Wood's-metal bath at 220-225°. When CO_2 evolution was finished, the melt was cooled and then dissolved in 16 ml of chloroform, the solution washed several times with 5% soda solution, the chloroform extract dried with anhydrous Na_2SO_4, and the chloroform distilled off. There was obtained 3.65 g (88.16%) of 2-phenyl-1,5-pentamethylenimidazole, m.p. 132-134°; after crystallization from ether (1 : 80), m.p. 132.5-134.5° (tablets). The substance was slightly soluble in water, more soluble in ether and ethyl acetate, and readily soluble in chloroform, benzene, acetone, and methanol.

Found %: N 13.08, 13.34. $C_{14}H_{16}N_2$. Calculated %: N 13.20.

Hydrolysis of methyl 2-phenyl-1,5-pentamethylenimidazole-4-carboxylate. a) Alkaline hydrolysis. A 3.5 g quantity of methyl 2-phenyl-1,5-pentamethylenimidazole-4-carboxylate was heated for 1 hr at 60° with 10 ml of 10% potassium hydroxide solution, the unreacted methyl ester (2.1 g) filtered out, and the filtrate acidified in the cold with 10% hydrochloric acid to a pH of about 6.5; after extraction with chloroform there was obtained 1.3 g (98.4%, reckoned on the reacted ester) of 2-phenyl-1,5-pentamethylenimidazole-4-carboxylic acid, m.p. 164-165° after crystallization.

b) Acid hydrolysis. A 10.2 g quantity of methyl 2-phenyl-1,5-pentamethylenimidazole-4-carboxylate was boiled for 7 hr in 50 ml of 15% hydrochloric acid, 0.5 g of charcoal being added to the solution 1 hr before the end of the reaction. The hot solution was filtered; on cooling, 9.3 g (77%) 2-phenyl-1,5-pentamethylenimidazole-4-carboxylic acid hydrochloride sesquihydrate, m.p. 238-240°, separated out.

Found: on titration with 0.1 N NaOH solution (phenolphthalein), 328. Weight loss on drying at 120°: % H_2O 6.6. $C_{15}H_{16}O_2N_2 \cdot HCl \cdot 1.5\ H_2O$. Calculated: M 319.5; % H_2O 8.5.

The hydrochloride of (IV) was obtained also by dissolving (IV) in 15% hydrochloric acid with heating; yield 80%, m.p. 238.5-240°.

Esterification of 2-phenyl-1,5-pentamethylenimidazole-4-carboxylic acid to the methyl ester (V). A 7.8 g quantity of the acid was boiled for 4 hr in 50 ml of an 18% solution of HCl in methanol. The methanol was distilled off and the residue dissolved in the cold in 20 ml of water and neutralized with saturated soda solution to pH 7.5; in this case 5.55 g (67.52%) of ester (V), m.p. 160-162°, separated out. When the mother liquor was acidified with 15% hydrochloric acid to pH 6 and then extracted with chloroform, 1.2 g (15.38%) of unreacted acid (IV) was obtained.

α-(2'-Homopiperidylene)nitromethane. A mixture of 152.4 g of O-methylcaprolactim and 73.2 g of nitromethane was boiled intermittently for 26 hr, and the resulting precipitate was filtered out and washed with 50 ml of ether. There was obtained 126.3 g of α-(2'-homopiperidylene)nitromethane, m.p. 89-91°. The ether was distilled from the washings, and the residue was boiled for 22 hr more, another 11.8 g of the substance, m.p. 86-90°, being isolated; on crystallization from water (1 : 6) this gave 10.1 g of the substance in the form of hexagonal tablets with m.p. 89-91°.* Total yield 136.4 g (72.86%). The substance was slightly soluble in ether and more soluble in benzene, chloroform, acetone, alcohol, and ethyl acetate. When O-methylcaprolactim was condensed with nitromethane in the presence of sodium methoxide [2], the yield of α-(2'-homopiperidylene)nitromethane was only 10%.

SUMMARY

1. O-Methylcaprolactim can easily be condensed with 2-phenyloxazolone-5, as well as hippuric acid in the presence of acetic anhydride, with the formation of 2-phenyl-4-(2'-homopiperidylen)oxazolone-5.

2. On alcoholysis of 2-phenyl-4-(2'-homopiperidylen)oxazolone-5 in methanol in the presence of potassium hydroxide, the oxazolone is converted to 2-phenyl-1,5-pentamethylenimidazole-4-carboxylic acid.

3. α-Benzoylamino-β-(2'-homopiperidylene)acrylic acid must be regarded as an intermediate product in this rearrangement.

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ALKAMINE ESTERS OF α,ω-DIPHENYLALKYLCARBOXYLIC ACIDS

III. DERIVATIVES OF β-PHENYL-α-(p-METHOXYPHENYL)PROPIONIC, α,β-DIPHENYLPROPIONIC, AND α,γ-DIPHENYLBUTYRIC ACIDS

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1860-1866, June, 1960
Original article submitted June 9, 1959

As was shown in the preceding article [1], alkamine esters of β-(p-methoxyphenyl)-α-phenylpropionic acid have considerable biological activity; in this case the alkamine esters are active mainly as spasmolytics, whereas the tropine ester has marked adrenolytic action. In order to determine the effect of the methoxyl group on the biological activity with respect to the position of the substituted phenyl radical in the propionic chain, β-phenyl-α-(p-methoxyphenyl)- and α,β-diphenylpropionic acids were synthesized, and their alkamine esters and amides were prepared. It was found•• that all alkamine esters except tropine ones have spasmolytic action, dilate the blood vessels of an isolated rabbit ear, decrease the tonus of a segment of intestine, and manifest elements of n-cholinolytic activity. Despite the differences in structure of the acids, the alkamine esters are similar to one another in their biological properties, which differ somewhat from those of the corresponding β-(p-methoxyphenyl)-α-phenylpropionic acid esters in that the latter are less toxic and display a sedative effect. As regards the tropine esters of the acids investigated, they all have marked adrenolytic action, lower the blood pressure, and have sympatholytic action. The tropine ester of β-phenyl-α-(p-methoxyphenyl)propionic acid is much weaker in its action than that of β-(p-methoxyphenyl)-α-phenylpropionic acid. This effect of transposition of the methoxyphenyl and phenyl radicals on the biological properties may be ascribed to the resulting proximity of two oxygen-containing functions: CH_3O and COOR, which probably facilitates the more rapid metabolism of the compound in the organism.

β-Phenyl-α-(p-methoxyphenyl)propionic acid was synthesized, proceeding from p-methoxyphenylacetonitrile and benzyl chloride in the presence of sodium amide

$$p\text{-}CH_3OC_6H_4CH_2CN + C_6H_5CH_2Cl \xrightarrow{NaNH_2} p\text{-}(CH_3O)C_6H_4CH(CH_2C_6H_5)CN.$$

The dibenzyl-substituted $p\text{-}(CH_3O)C_6H_4C(CH_2C_6H_5)_2CN$••• was formed in considerable quantity at the same time. A peculiarity of this nitrile is that it is not hydrolyzed by ordinary procedures either in an alkaline or an acid medium. We managed to obtain a small amount of α-benzyl-α-(p-methoxyphenyl)-β-phenylpropionamide, only by prolonged heating with 70% H_2SO_4. Such passivity of this trisubstituted acetonitrile is evidently due to the screening action of the three relatively large substituent radicals.

• Deceased.

••The pharmacological study of the compounds which we synthesized was carried out in the Pharmacology Department of our Institute under the direction of M. D. Mashkovskii by co-workers S. S. Liberman, K. A. Zaitseva, and G. S. Arutyunyan, to whom we extend out sincere thanks.

•••It should be noted that A. Meyer [2] was unable to introduce a second benzyl group into benzyl cyanide.

α,β-Diphenylpropionic acid was prepared by hydrogenating trans-α,β-diphenylacrylic acid [3] in sodium hydroxide solution in the presence of Raney nickel. The yield of diphenylpropionic acid was nearly quantitative.

The alkamine (including the tropine) esters of the indicated acids were prepared by condensing their acid chlorides with the corresponding aminoalcohols [1]. In some cases a sufficiently pure ester hydrochloride was isolated directly, whereas in others it was necessary to proceed through the base, which was purified by distillation in vacuo. The diethylaminoalkylamides of these acids were obtained in this way.

On continuing the investigation of the effect on the biological properties of the disposition of the two phenyl radicals along the length of the alkane acid chain, by increasing the distance between them, beginning with derivatives of diphenylacetic acid and passing through α,β-diphenylpropionic acid, we found it necessary to synthesize and to study α,γ-diphenylbutyric acid. To prepare the latter we used the condensation [4] of β-phenylethyl bromide with the Na derivative of phenylacetonitrile and subsequent hydrolysis of the nitrile formed. Alkamine esters of α,γ-diphenylbutyric acid also proved to be biologically active: they had spasmolytic action, but less pronounced. The tropine ester had adrenolytic activity which also was much less pronounced than that of the tropine ester of β-(p-methoxyphenyl)-α-phenylpropionic acid; however, its nicotinolytic action was stronger.

The diethylaminoethylamides prepared from all three diphenylalkylcarboxylic acids were distinguished by their high toxicity and weak local-anesthetic action.

EXPERIMENTAL

α-(p-Methoxyphenyl)-β-phenylpropionitrile. To 6.45 g of powdered sodium amide in 150 ml of dry benzene in a three-neck flask with mechanical stirring, 22 g of p-methoxyphenylacetonitrile* was quickly added; the mixture was heated at 90° in a bath for 25-30 min, after which the reaction mass was cooled; 20.85 g of benzyl chloride was then added dropwise during 30 min; stirring was continued for 8 hr more at room temperature, after which the mixture was poured into water, the benzene layer was separated, the water layer extracted twice with benzene, the extracts added to the main solution, and the combined solution washed with water until it ceased to give an alkaline reaction. It was then dried, the benzene driven off, and the residue distilled at 1.5 mm. There was collected 14.1 g (39.2%) of a fraction with b.p. 182-185°, which crystallized. M.p. 66.5-67.5°. It was readily soluble in ether and acetone and less so in alcohol.

Found %: C 81.13, 80.91; H 6.58, 6.48; N 6.20, 6.40. $C_{16}H_{15}ON$. Calculated %: C 81.01; H 6.33; N 5.90.

From the still-pot residue 6.8 g (13.9%) of a white, crystalline substance was isolated, which crystallized from alcohol in the form of rectangular tablets with m.p. 111-112.5°.

Found %: C 84.12, 84.06; H 6.56, 6.33; N 4.22, 4.53. $C_{23}H_{21}ON$. Calculated %: C 84.40; H 6.42; N 4.25.

Analytical data corresponded to α,α-dibenzyl-p-methoxyphenylacetonitrile. Owing to the excess of sodium amide and benzyl chloride, this nitrile was preferentially formed. Neither boiling with aqueous or alcoholic alkali, nor boiling with dilute strong acids led to hydrolysis products. A small yield of a white, crystalline substance with m.p. 180-182° (from alcohol), corresponding to α,α-dibenzyl-p-methoxyphenylacetamide, was obtained only on heating for 9 hr with mechanical stirring at a bath temperature of 140-150°.

Found %: N 4.02. $C_{23}H_{23}O_2N$. Calculated %: N 4.06.

Hydrolysis of α-(p-methoxyphenyl)-β-phenylpropionitrile. A mixture of 2.5 g of this nitrile, 1.7 g of potassium hydroxide, 1.7 ml of water, and 7 ml of alcohol was refluxed, with stirring, for 9 hr and left overnight. On the next day the separated crystals, which had the form of fine, rectangular tablets, were filtered out and washed with water, alcohol, and ether. After recrystallization from alcohol 0.35 g (13%), m.p. 159.5-161°, was obtained. Its analysis corresponded to α-p-methoxyphenyl-β-phenylpropionamide.

Found %: C 75.11, 75.55; H 6.81, 6.74; N 5.79, 5.95. $C_{16}H_{17}O_2N$. Calculated %: C 75.29; H 6.66; N 5.49.

*p-Methoxyphenylacetonitrile was prepared from anisaldehyde [5] through anisyl alcohol and anisyl chloride. Attempts to prepare it through the chloromethylation of anisole [6] gave an impure nitrile. p-Methoxyphenylacetic acid, obtained by hydrolysis of the nitrile, had m.p. 86.5° in the first case and 68.71° in the second.

The filtrate was evaporated in vacuo. The residue, a viscous, yellow mass, was dissolved in water and the aqueous solution washed several times with ether, filtered, and acidified with hydrochloric acid. The light oil which separated crystallized on trituration. The crystals were filtered out, washed on the filter with water, and dried in vacuo over sulfuric acid. There was obtained 2.05 g (76%). M.p. 104.5-106°. The α-(p-methoxyphenyl)-β-phenylpropionic acid was very slightly soluble in water, readily soluble in alcohol, and still more soluble in ether.

Found %: C 74.57, 74.75; H 5.99, 6.06. $C_{16}H_{16}O_3$. Calculated %: C 75.00; H 6.25.

Ethyl α-(p-methoxyphenyl)-β-phenylpropionate. A solution of 12 g of the acid obtained above, in 120 ml of ethanol and 12 ml of concentrated sulfuric acid, was boiled for 9 hr. The alcohol was distilled off in vacuo in a water bath and the residue diluted with water, neutralized with 10% soda solution, and extracted with ether. The extract was dried with anhydrous sodium sulfate. The solvent was driven off, and the residue was distilled at 2 mm. The 170-171° fraction was collected. Yield 11.63 g (87%).

Found %: C 76.03; H 7.04. $C_{18}H_{20}O_3$. Calculated %: C 76.05; H 7.04.

α-(p-Methoxyphenyl)-β-phenylpropionyl chloride. A mixture of 15 g of the acid obtained above and 9 g of thionyl chloride was heated for 2 hr at 70°. Within 15 min after heating began, the acid dissolved. The excess $SOCl_2$ was distilled off in vacuo. The residue crystallized, m.p. 64-66° from petroleum ether. It was readily soluble in ether and benzene. Yield 14 g (87%).

Found %: Cl 12.94. $C_{16}H_{15}O_2Cl$. Calculated %: Cl 12.91.

2-N,N-Diethylaminoethyl α-(p-methoxyphenyl)-β-phenylpropionate. A mixture of 5 g of the acid chloride obtained above, 8 g of 2-N,N-diethylaminoethanol, and 10 ml of dry benzene was boiled for 4 hr with stirring; the benzene and excess diethylaminoethanol were distilled off in vacuo, and the residue was dissolved in water and treated with soda solution. The oil which separated was extracted with ether, the extract dried with anhydrous sodium sulfate, the ether driven off, and the residue distilled at 2 mm. Four g (61.9%) of the 206-207° fraction was collected; it was an oily liquid, readily soluble in alcohol and ether.

Found %: N 3.97. $C_{22}H_{29}O_3N$. Calculated %: N 3.94.

The hydrochloride was a white, crystalline substance. M.p. 122-124° (from light benzine).

Found %: Cl 8.78, 8.94. $C_{22}H_{30}O_3NCl$. Calculated %: Cl 9.05.

3-N,N-Diethylaminopropyl α-(p-methoxyphenyl)-β-phenylpropionate was prepared like the preceding. B.p. 220-222° (1.5 mm).

Found %: N 3.99. $C_{23}H_{31}O_3N$. Calculated %: N 3.79.

The hydrochloride was a white, crystalline substance. M.p. 122-123.5° (from benzene).

Found %: Cl 8.74; N 3.58. $C_{23}H_{32}O_3NCl$. Calculated %: Cl 8.75; N 3.45.

Tropine α-(p-methoxyphenyl)-β-phenylpropionate. A mixture of 10.5 g of α-(p-methoxyphenyl)-β-phenylpropionyl chloride, 4.73 g of tropine, and 30 ml of dry benzene was heated at 70-75° for 17 hr. On cooling, the precipitate formed was filtered out, and washed with dry ether. The hydrochloride obtained was dissolved in water and treated with 50% potash solution. The oily base which separated crystallized on trituration. It was filtered out, washed with water, and dried in vacuo over solid alkali. Yield 10.18 g (70%). M.p. 92-92.5° (from alcohol).

Found %: C 76.07; H 8.00; N 3.79. $C_{24}H_{29}O_3N$. Calculated %: C 75.94; H 7.70; N 3.69.

The hydrochloride consisted of crystals with m.p. 190-192° (from a chloroform—ether mixture), very soluble in water.

Found %: Cl 8.54. $C_{24}H_{30}O_3NCl$. Calculated %: Cl 8.54.

α-(p-Methoxyphenyl)-β-phenylpropionic 2-N,N-diethylaminoethylamide. To 3.4 g of N,N-diethylethylenediamine in 10 ml of benzene, a solution of 6 g of α-(p-methoxyphenyl)-β-phenylpropionyl chloride was added dropwise with stirring, after which the mixture was heated in a water bath at 75-80° for 3 hr with continued stirring. Then the benzene was distilled off in vacuo, the residue treated with 5% hydrochloric acid, and the acid solution extracted several times with ether and made alkaline with 10% sodium hydroxide solution. The amide base which

separated out was extracted with ether. The extract was dried with potash and the ether distilled off. The residue crystallized. The crystals were readily soluble in chloroform and alcohol and somewhat less soluble in ether; m.p. 61-62° (from anhydrous ether).

Found %: N 7.75. $C_{22}H_{30}O_2N_2$. Calculated %: N 7.93.

The hydrochloride was a more crystalline substance, m.p. 122-123° (from ethyl acetate), readily soluble in water and alcohol.

Preparation of a quaternary salt of α-(p-methoxyphenyl)-β-phenylpropionic 2-N,N-diethylaminoethylamide. A 5.45 g quantity of α-(p-methoxyphenyl)-β-phenylpropionic 2-N,N-diethylaminoethylamide was dissolved with slight heating (30-40°) in a small amount of dry acetone. The solution was cooled, and 1.1 ml of methyl iodide was added. The mixture was heated at 42-45° for 2 hr with stirring. On cooling, a crystalline substance separated. The latter was filtered out, and recrystallized from anhydrous alcohol. Yield 6.3 g, m.p. 148-149.5°. It was insoluble in ether and benzene and soluble in water and acetone.

Found %: I 25.83. $C_{23}H_{33}O_2N_2I$. Calculated %: I 25.59.

α,β-Diphenylpropionic acid. Condensation [3] of benzaldehyde with sodium phenylacetate for 15 hr in a boiling acetic anhydride medium gave trans-α,β-diphenylacrylic acid, m.p. 170-172°, which was then hydrogenated with Raney nickel at 50-60 atm in an aqueous-alkali medium.. The yield of α,β-diphenylpropionic acid was nearly quantitative. M.p. 82°. •

α,β-Diphenylpropionyl chloride was obtained by heating the acid with thionyl chloride. B.p. 140-142° (2 mm). ••

Found %: Cl 14.51, 14.48. $C_{15}H_{13}OCl$. Calculated %: Cl 14.50.

Treatment of the acid chloride obtained with aqueous NH_3 solution gave α,β-diphenylpropionamide, m.p. 133-134° (from water).

Found %: C 79.72, 79.73; H 6.60, 6.70; N 6.20, 6.22. $C_{15}H_{15}ON$. Calculated %: C 80.00; H 6.71; N 6.22.

Tropine α,β-diphenylpropionate hydrochloride. A solution of 10.4 g of the acid chloride described above, in 20 ml of dry benzene was added dropwise, with stirring, to a solution of 6 g of tropine in 20 ml of benzene. The mixture was then heated for 6 hr in a glycerol bath at 85-90° (in the bath). On the next day the resulting precipitate was filtered out, washed with benzene and ether, and dried. Yield 12 g (75%). M.p. 186-192° (decomp.), m.p. 194-195° (from anhydrous propanol-2).

Found %: C 71.48, 71.16; H 7.19, 7.21; Cl 9.31. $C_{23}H_{28}O_2NCl$. Calculated %: C 71.56; H 7.05; Cl 9.19.

2-N,N-Diethylaminoethyl α,β-diphenylpropionate was obtained by adding a solution of 30.6 g of the acid chloride in 65 ml of benzene to a solution of 15 g of 2-N,N-diethylaminoethanol in 50 ml of benzene and heating for 6 hr at 80° in the bath. The resulting clear solution was treated with water, the water layer separated, and the benzene layer washed twice with water; the washings were added to the main solution. The combined water layer was purified by extraction with ether and then made alkaline to thymolphthalein by treatment with 5% potassium hydroxide solution, and the base which separated out was extracted with ether, the ethereal extract dried with anhydrous sodium sulfate, the ether driven off, and the residue distilled. B.p. 173-180° (2 mm). Yield 33.4 g (82%).

Found %: C 77.41, 77.12; H 8.26, 8.21. $C_{21}H_{27}O_2N$. Calculated %: C 77.48; H 8.36.

The hydrochloride was obtained by treating an ethereal solution of the base with a 30% solution of HCl in absolute alcohol. The precipitated crystals were washed on the filter with dry ether and dried in vacuo over H_2SO_4. Yield 96%. M.p. 110-112°.

Found %: Cl 9.97. $C_{21}H_{28}O_2NCl$. Calculated %: Cl 9.80.

3-N,N-Diethylaminopropyl α,β-diphenylpropionate was similarly obtained from 3-N,N-diethylaminopropanol and α,β-diphenylpropionyl chloride. B.p. 151-155° (1-1.5 mm).

• α,β-Diphenylpropionic acid has three crystalline modifications with m. pts. 82, 88-89, and 95-96° [7].
••B.p. 177° (14 mm) is given in the literature [8].

Hydrochloride, m.p. 138-140°. It was readily soluble in water.

Found %: C 70.33; H 8.08; N 3.80; Cl 9.43. $C_{22}H_{30}O_2NCl$. Calculated %: C 70.51; H 8.04; N 3.72; Cl 9.43.

α,γ-Diphenylbutyryl chloride was prepared by heating α,γ-diphenylbutyric acid [4] with thionyl chloride for 2.5 hr. When the excess thionyl chloride was driven off, a crystalline precipitate remained; m.p. 31.5-33.5° (from petroleum ether). It was readily soluble in ether and benzene.

Found %: Cl 13.67, 13.38; C 74.52, 74.59; H 6.02, 5.95. $C_{16}H_{15}OCl$. Calculated %: Cl 13.65; C 74.27; H 5.80.

2-N-N-Diethylaminoethyl α,γ-diphenylbutyrate. A mixture of 5 g of the acid chloride prepared above, 8.8 g of 2-N,N-diethylaminoethanol, and 100 ml of dry benzene was heated, with stirring, for 5 hr at 80° in the bath, and the benzene and excess alcohol were then distilled off in vacuo. The residue was dissolved in 5% hydrochloric acid, washed several times with ether, and made alkaline to thymolphthalein with sodium hydroxide solution. The base which separated out was extracted with ether, the ethereal extract dried, the ether driven off, and the residue distilled. The 215-216° (4 mm) fraction, a viscous liquid, was collected. Yield 5.27 g (77.5%). The base was converted to the oxalate, m.p. 103.5-105°, which dissolved readily in water and was crystallized from alcohol.

Found %: C 67.02, 67.00; H 7.30, 7.28; N 3.27, 3.38. $C_{22}H_{29}O_2N \cdot (COOH)_2$. Calculated %: C 67.13; H 7.22; N 3.26.

3-N,N-Diethylaminopropyl α,γ-diphenylbutyrate was prepared like the preceding. On distillation of the base the 181-182° (1.5 mm) fraction, a viscous oil, was collected. Yield 5.25 g (68%). The oxalate consisted of colorless crystals with m.p. 130.5-132°.

Found %: C 67.71, 67.52; H 7.45, 7.44; N 3.11, 3.31. $C_{23}H_{31}O_2N \cdot (COOH)_2$. Calculated %: C 67.72; H 7.65; N 3.16.

Tropine α,γ-diphenylbutyrate hydrochloride. A mixture of 10 g of α,γ-diphenylbutyryl chloride, 4.9 g of tropine, and 40 ml of dry benzene was heated, with stirring, for 40 hr at 85-90° in the bath. The resulting precipitate was filtered out, and washed with dry benzene. Yield 10.8 g (68-70%), m.p. 173-5-174°. The hydrochloride was dissolved in anhydrous alcohol and precipitated with ether. M.p. 177.5-178.5°. It was readily soluble in alcohol and water and less soluble in ethyl acetate.

Found %: Cl 8.79, 8.70; N 3.55, 3.63. $C_{24}H_{30}O_2NCl$. Calculated %: Cl 8.88; N 3.50.

α,γ-Diphenylbutyric 2-N,N-diethylaminoethylamide was prepared like α,β-diphenylpropionic 2-N,N-diethylaminoethylamide. Melting point of the base, 33.5-35°. It was readily soluble in benzene, alcohol, and ether. The base was converted to the oxalate, m.p. 113-114° (from alcohol), soluble in water.

Found %: C 67.60, 67.76; H 7.67, 7.50; N 6.52. $C_{24}H_{32}O_5N_2$. Calculated %: C 67.29; H 7.47; N 6.54.

SUMMARY

1. All the prepared alkamine esters and amides of α-(p-methoxyphenyl)-β-phenylpropionic, α,β-diphenylpropionic, and α,γ-diphenylbutyric acids have considerable pharmacological action.

2. Introduction of a p-methoxyl group into α-phenyl or β-phenyl does not qualitatively change the biological properties of alkamine esters; quantitatively, α-(p-methoxyphenyl) weakens the manifestation thereof.

3. Increase of the distance between substituent phenyl groups along the alkane chain by one CH_2 link leads to weakening of the pharmacological action.

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OXIDATION OF β-KETOACETALS BY LEAD TETRAACETATE

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1866-1872,
June, 1960
Original article submitted June 11, 1959

β-Ketoacetals $ROOCH_2CH(OR')_2$ are available, highly reactive compounds [1-4] and are coming to be ever more widely used in synthetic chemistry. Moreover, some of their reactions, which open up new possibilities, have scarcely been investigated as yet. The least-studied aspect of β-ketoacetal chemistry is the question of the reactivity of their central methylene link and, in particular, the replacement of the hydrogen atoms of this link. The only reaction of this type that has been investigated in detail is the recently studied bromination of β-ketoacetals [5, 6].

The present article is devoted to the oxidation of β-ketoacetals by lead tetraacetate. As reported briefly by us [5] and independently by other authors [7, 8], we were able to introduce the oxygen function into the methylene link of β-ketoacetals in this way; however, the details of this reaction remained unknown. Only recently, when our work was nearly finished, an article appeared [9], which dealt in more detail with this process in the very simple case of the oxidation of acetoacetaldehyde dimethyl acetal.

Our efforts were directed primarily toward establishing the structure of the reaction product. As earlier authors [7-9] indicated without direct proof, the reaction is accompanied not only by introduction of an acetoxyl group in the central methylene link, but also by exchange of one of the methoxyl radicals of the acetal grouping with the formation of an α-acetoxy-β-ketoacylal.*

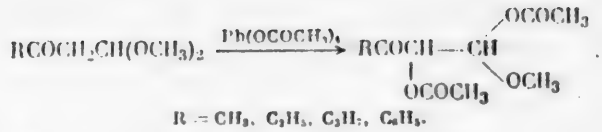
$$CH_3COCH_2CH(OCH_3)_2 \xrightarrow{Pb(OCOCH_3)_4} CH_3CO-\underset{\displaystyle OCOCH_3}{\underset{|}{CH}}-\overset{\displaystyle OCH_3}{\overset{/}{\underset{\displaystyle OCOCH_3}{\backslash}}}CH$$

Our determination of acetoxyl groups in the oxidation product showed the presence of two acetoxyls and thereby directly confirmed the structure of the oxidation product. This rather unexpected result cannot be explained by simple exchange of one of the acetal methoxyl groups by acetoxyl under the influence of the acetic acid medium in which the reaction was carried out [comp. 10], since we obtained a similar product on oxidation in benzene solution. The result of the reaction is directly connected with its mechanism, which is discussed below.

The oxidation of β-ketoacetals is quite general in scope; it may be applied to β-ketoacetals of both the aliphatic and aromatic series.

It is most conveniently carried out in glacial acetic acid solution, although it also can be done in benzene, it being necessary to use at least a 50% excess of lead tetraacetate and to heat the reaction mixture. It is absolutely

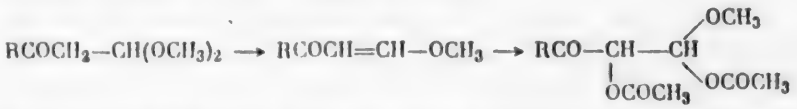
*Data of elementary analysis for this substance and the "normal" oxidation product—an α-acetoxy-β-ketoacetal—are very nearly the same and do not provide the possibility of reaching an unambiguous conclusion on the structure of the substance obtained.



R = CH_3, C_2H_5, C_3H_7, C_4H_9.

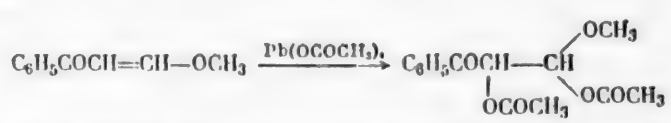
necessary to filter the reaction product before vacuum distillation. When ethylene acetals, which are more convenient in other reactions [4], are used in this reaction, a complex mixture of substances is formed.

The apparently anomalous result of the reaction leading not to an α-acetoxy-substituted acetal but instead to the corresponding acylal throws some light on its mechanism. We assumed that under the reaction conditions an alcohol molecule is first split off from the β-ketoacetal, after which the β-methoxyvinyl ketone undergoes oxidation at the double bond, adding on two acetoxyl groups.



There are no objections to this scheme, since the reverse transition between β-ketoacetals and alkoxyvinyl ketones is well known and has been observed under various conditions [11]. Furthermore, this agrees with some of our data. Thus, for instance, when equimolar quantities of reagents are used, only half the acetal is oxidized, while all the quadrivalent lead is reduced to bivalent, which apparently is due to its consumption in the oxidation of the alcohol formed. The negative results obtained in the oxidation of ethylene acetals also become understandable, since the first step of the process in this case must be the formation of a polyfunctional vinyl ether of the type $RCOCH=CH-O-CH_2CH_2OH$, which under the reaction conditions will itself undergo further complex conversions, which in turn complicate the final result. At the same time the great stability of ethylene acetals [4] hinders the first step of the process—elimination of the alcohol—and as a result, oxidation goes more slowly in the case under consideration.

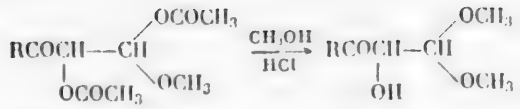
We also confirmed the proposed scheme by direct facts. It was found that β-methoxyvinyl ketones are also oxidized by lead tetraacetate under the conditions of our reaction, identical oxidation products—α-acetoxy-β-ketoacetals—being formed.



Moreover, we were able to prove that β-methoxyvinyl ketones actually are formed in the reaction mixture on oxidation of β-ketoacetals. Since direct isolation of this compound from the reaction mixture proved to be very difficult, we identified it through the reaction of mercuric acetate with vinyl ethers, described earlier [12]. It was found that, while neither the original β-ketoacetal nor the main reaction product—the α-acetoxy-β-ketoacylal—reacts with mercuric acetate, methyl β-methoxyvinyl ketone does react with the mercury salt, forming a stable, crystalline substance.* We isolated an identical substance on treating the reaction mixture, obtained by oxidizing an excess of acetoacetaldehyde dimethyl acetal by means of lead tetraacetate, with mercuric acetate. This proves that a β-methoxyvinyl ketone is formed in the reaction and thereby confirms the mechanism of β-ketoacetal oxidation proposed by us. It is very probable that these data may prove useful in discussion of the mechanism of oxidation of other carbonyl compounds by the same oxidizing agent. In particular, the oxidation of ketones to α-acetoxyketones may proceed through the enol form with subsequent addition of acetoxyl groups at the double bond.

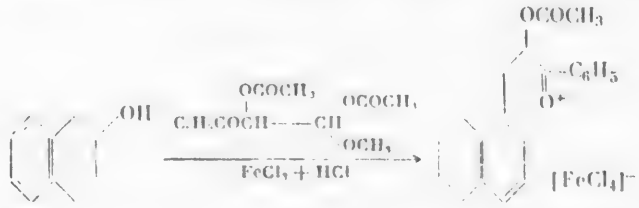
Our convenient method for the synthesis of α-acetoxy-β-ketoacylals, on whose chemical properties there was practically no information until recently, made it possible to study some of their reactions. It was of considerable interest to use substituted acylals for α-hydroxy-β-ketoacetal preparation. This transition was easily carried out by treating the acylals with methanolic hydrogen chloride solution.

*We did not establish the structure of this substance, but in all probability it is one of the conversion products of the α-acetoxymercuri-β-ketoaldehyde.

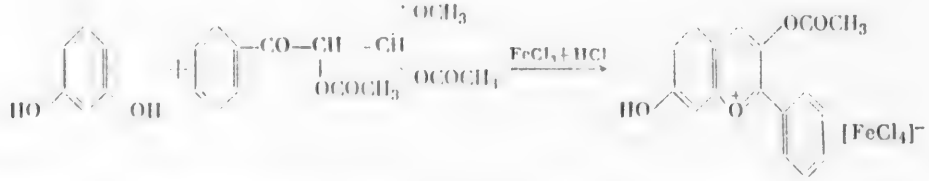


Yields of α-hydroxy-β-ketoacetals amount to 35-65%, and the method of their synthesis, described here, is quite convenient in the preparative respect. The synthesis of the simplest of these—α-hydroxy-β-ketobutanal acetal—by the same route has just been described (independently) by other authors [9].

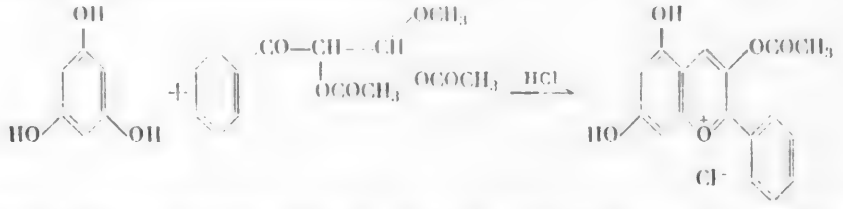
Of the possibilities which α-acetoxy-β-ketoacylals present for the preparation of heterocyclic compounds, their use for the synthesis of pyrylium salts containing the acetoxyl group seemed the most interesting, these salts being the nearest derivatives of natural anthocyanines. It was found that, like other derivatives of β-ketoaldehydes [6], α-acetoxy-β-ketoacylals smoothly react with β-naphthol in the presence of ferric chloride in acetic acid to form naphthopyrylium salts. Thus α-acetoxybenzoylacetaldehyde acylal gave 3-acetoxy-2-phenylnaphtho-[1, 2 : 5, 6]pyrylium ferrichloride.



Its UV spectrum is similar to those of other naphthopyrylium salts [13]. The wholly analogous α-acetoxybenzoylacetaldehyde acylal reacts under these conditions with resorcinol [14], forming 3-acetoxy-7-hydroxyflavylium ferrichloride.



In the reaction of acylals with phloroglucinol, as in the case of β-chlorovinyl ketones [14], ferric chloride is unnecessary, and the condensation takes place even in the presence of hydrogen chloride, 3-acetoxy-5,7-dihydroxyflavylium chloride (3-acetoxychrysinidin) being formed.



The substance obtained is extremely unstable, and it was very difficult to isolate in analytically pure form; condensation in the presence of ferric chloride led to complete resinification for the same reason.

Attempts to prepare 3-hydroxyflavylium salts by condensation of α-hydroxy-β-ketoacetals with resorcinol or phloroglucinol under these same conditions have given no positive result as yet.

The data given in this article show that α-acetoxy-β-ketoacylals are now available compounds and are of undoubted interest, especially for the synthesis of certain scarcely available heterocyclic compounds.

EXPERIMENTAL

β-Methoxy-α, β-diacetoxyethyl methyl ketone. A mixture of 12 g of acetoacetaldehyde dimethyl acetal and 41 g of lead tetraacetate in 41 ml of glacial acetic acid was gradually heated to 60-65° with vigorous stirring and the reaction was carried out at this temperature for 6-7 hr, until a negative test for quadrivalent lead (with

water) was obtained. Then the acetic acid was distilled off in a slight vacuum and the residue treated with water and benzene. The water layer was extracted several times with benzene. The benzene extracts were dried over magnesium sulfate. After driving off the solvent, the remaining turbid oil was filtered, and distilled in vacuo. There was obtained 3 g of the original acetal (b.p. 67-69° at 15 mm) and 5.2 g (37%, reckoned on the reacted acetal) of a substance with b.p. 142-145° (15 mm); after redistillation it had:

B.p. 144-145° (15 mm), $n^{20}D$ 1.4361, d^{20}_4 1.1410.

Found %: C 49.63, 49.66; H 6.92, 6.89. $C_9H_{14}O_6$. Calculated %: C 49.52; H 6.42.

Literature data [9]: b.p. 142-144° (13 mm), $d^{20}D$ 1.4398.

β-Methoxy-α, β-diacetoxyethyl ethyl ketone. In analogy with the preceding experiment, 22 g of propioacetaldehyde dimethyl acetal and 70 g of lead tetraacetate in 70 ml of glacial acetic acid gave 10 g of the original acetal and 11 g (58%, reckoned on the reacted acetal) of a substance with b.p. 123-128° (8 mm); after redistillation it had:

B.p. 128-129° (9 mm), $n^{20}D$ 1.4359, d^{20}_4 1.1102.

Found %: C 52.01, 52.03; H 7.26, 7.25. $C_{10}H_{16}O_6$. Calculated %: C 51.98; H 6.93.

Determination of acetoxyl groups in β-methoxy-α, β-diacetoxyethyl ethyl ketone. A 0.2730 g quantity of β-methoxy-α, β-diacetoxyethyl ethyl ketone in 3 ml of sulfuric acid (1 : 2) was refluxed in a flask for 2 hr, and the acetic acid formed was removed by steam distillation. The distillate was titrated with sodium hydroxide solution (0.15535 N), phenolphthalein being used. Fifteen ml of alkali was consumed; the calculated value was 15.3 ml of alkali for two acetoxyl groups or 8.7 ml of alkali for one acetoxyl group.

β-Methoxy-α, β-diacetoxyethyl propyl ketone. In analogy with the preceding experiments, 30 g of butyroacetaldehyde dimethyl acetal and 90 g of lead tetraacetate in 65 ml of glacial acetic acid gave 10 g of the original acetal and 13 g (42.5%, reckoned on the reacted acetal) of a substance with b.p. 106-109° (1 mm); after redistillation it had:

B.p. 107-108° (1 mm), $n^{20}D$ 1.4380, d^{20}_4 1.1052.

Found %: C 53.53, 53.58; H 7.62, 7.63. $C_{11}H_{16}O_6$. Calculated %: C 53.70; H 7.32.

β-Methoxy-α, β-diacetoxypropiophenone. a) In analogy with the preceding experiments, 9.3 g of benzoylacetaldehyde dimethyl acetal and 23 g of lead tetraacetate in 16 ml of glacial acetic acid gave 4 g of the original acetal and 4 g (52.2%, reckoned on the reacted acetal) of a substance with b.p. 161-163° (3 mm). After standing for 3 months in a refrigerator the substance crystallized: m.p. 48-49.5° (after washing many times with hexane).

b) A mixture of 5.7 g of phenyl β-methoxyvinyl ketone, 15 g of lead tetraacetate, and 20 ml of glacial acetic acid was stirred for 3 hr at 50°; 6.4 g (65%) of a substance with b.p. 150-151° (1 mm) was obtained. After long standing the substance crystallized: m.p. 47.5-48.5°.

A mixture test with the substance obtained in the preceding experiment gave no melting-point depression.

Found %: C 60.24, 60.18; H 5.89, 5.91. $C_{14}H_{16}O_6$. Calculated %: C 60.60; H 5.75.

Colorless needles, soluble in benzene, ether, acetone, and alcohol.

α-Hydroxy-β-ketovaleraldehyde dimethyl acetal. A mixture of 7.4 g of β-methoxy-α, β-diacetoxyethyl ethyl ketone and 20 ml of a 0.2 N solution of hydrogen chloride in anhydrous methanol was left for 3 days; the methanol was driven off in vacuo and the residue distilled. There was obtained 3.2 g (62%) of a substance with b.p. 86-88° (5 mm); after redistillation:

B.p. 80-81° (4 mm), $n^{20}D$ 1.4618, d^{20}_4 1.0931.

Found %: C 52.56, 52.51; H 8.16, 8.26. $C_7H_{14}O_4$. Calculated %: C 52.15; H 8.65.

α-Hydroxy-β-ketocaproaldehyde dimethyl acetal. In analogy with the preceding experiment, 13 g of β-methoxy-α β-diacetoxyethyl propyl ketone and 30 ml of a 0.25 N solution of hydrogen chloride in anhydrous methanol gave 6.1 g (65.5%) of a substance with b.p. 82-84° (3 mm); after subsequent distillations:

B.p. 83-84° (3 mm), $n^{20}D$ 1.4660, d^{20}_4 1.0809.

Found %: C 54.54, 54.58; H 9.08, 9.15. $C_8H_{16}O_4$. Calculated %: C 54.50; H 9.11.

α-Hydroxybenzoylacetaldehyde dimethyl acetal. In analogy with the preceding experiments, 4.8 g of α,β-diacetoxy-β-methoxypropiophenone and 15 ml of a 0.25 N solution of hydrogen chloride in methanol, after reacting for 3 weeks, gave 1.2 g (33.3%) of a substance with b.p. 99-101° (1 mm); after long standing in a refrigerator the substance crystallized: m.p. 37-39° (after washing with petroleum ether).

Found %: C 67.12, 67.07; H 6.74, 6.55. $C_{11}H_{14}O_4$. Calculated %: C 66.81; H 6.66.

Colorless crystals, readily soluble in common organic solvents.

2-Phenyl-3-acetoxynaphtho[1, 2 : 5, 6]pyrylium ferrichloride. A 3.2 g quantity of β-methoxy-α, β-diacetoxypropiophenone was mixed successively with a solution of 1.6 g of β-naphthol in 16 ml of glacial acetic acid in a solution of 5 g of ferric chloride in 7.5 ml of concentrated hydrochloric acid, and left for a day. The crystals which separated were recrystallized twice from glacial acetic acid. There was obtained 2.2 g (42%) of the ferrichloride, m.p. 180-182°.

Found %: C 49.47; H 3.05. $C_{21}H_{15}O_3Cl_4Fe$. Calculated %: C 49.20; H 2.93.

The crystals were brown; they were insoluble in benzene or ether, but dissolved gradually in glacial acetic acid.

3-Acetoxy-7-hydroxyflavylium ferrichloride. To a solution of 1 g of α,β-diacetoxy-β-methoxypropiophenone and 0.5 g of resorcinol in 7 ml of glacial acetic acid, a solution of 2.5 g of ferric chloride in 3.8 ml of concentrated hydrochloric acid was added, and the mixture was left for a day. The crystals which separated were washed with glacial acetic acid and recrystallized from the latter. There was obtained 2.6 g (74%) of a substance with m.p. 155-157°.

Found %: C 42.94, 42.87; H 3.12, 3.13. $C_{17}H_{13}O_4Cl_4Fe$. Calculated %: C 42.61; H 2.73.

Acicular, orange crystals, dissolving gradually in glacial acetic acid and insoluble in benzene, ether or chloroform.

5,7-Dihydroxy-3-acetoxyflavylium chloride. To a solution of 0.8 g of α,β-diacetoxy-β-methoxypropiophenone and 0.35 g of phloroglucinol in 8 ml of glacial acetic acid, 0.7 ml of concentrated hydrochloric acid was added. Immediately the reaction mixture changed color and red crystals separated; within 3 hr they were filtered out, washed many times with absolute ether, and dried. There was obtained 0.75 g (80%) of the chloride; it did not melt on heating above 250°.

Found %: C 62.43, 62.39; H 4.51, 4.31. $C_{17}H_{13}O_5Cl$. Calculated %: C 61.50; H 3.91.

Insoluble, red crystals. The substance was very unstable.

SUMMARY

1. A method for the synthesis of α-acetoxy-β-ketoacylals through the oxidation of β-ketoacetals by lead tetraacetate was developed.

2. A mechanism is proposed for this reaction, according to which it proceeds through the formation of an α-alkoxyvinyl ketone and subsequent acetoxylation of the latter by lead tetraacetate.

3. A method was developed for the synthesis of α-hydroxy-β-ketoacetals by treatment of α-acetoxy-β-ketoacylals with methanolic hydrogen chloride solution.

4. It was shown that α-acetoxy-β-ketoacylals react with polyhydric phenols or β-naphthol to form 3-acetoxy-substituted benzo- or naphthopyrylium salts.

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SYNTHESIS OF DERIVATIVES OF ISOXANTHINE

I. PREPARATION OF DIMETHYLISOXANTHINE AND ITS 8-CHLORO DERIVATIVE FROM 1,3,9-TRIMETHYLISOXANTHINE

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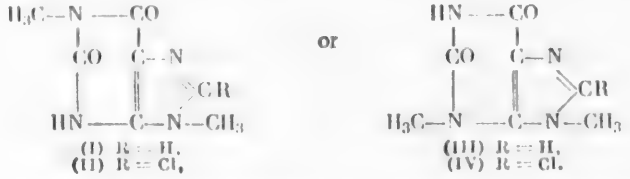
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1873-1878, June, 1960

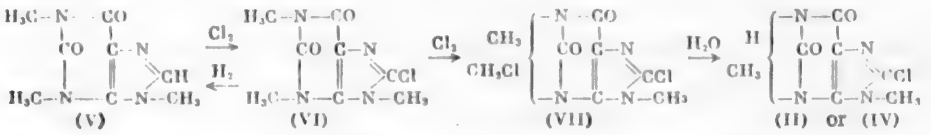
Original article submitted June 10, 1959

In the course of a preliminary study of the synthesis of new isoxanthine derivatives the problem arose of preparing dimethylisoxanthines and 8-chlorodimethylisoxanthines, in which one methyl group is attached to the N_9 atom of the imidazole part of the molecule, which thereby fixes the position of $\Delta^{7,8}$, while the other is on the N_1 or N_3 atom of the pyrimidine ring.



(I) R = H, (II) R = Cl, or (III) R = H, (IV) R = Cl.

A convenient and comparatively short method of synthesizing (II) or (IV) and also (I) or (III) appeared to be substitution with chlorine of the hydrogen in the C_8 position of 1,3,9-trimethylisoxanthine, i.e., isocaffeine (V), followed by partial demethylation of the resulting 8-chloroisocaffeine (VI) by introducing a second atom of chlorine into one of the methyl groups of the pyrimidine ring with subsequent hydrolytic splitting off of the chloromethyl group and then removal of the chlorine from the resulting 8-chlorodimethylisoxanthine.



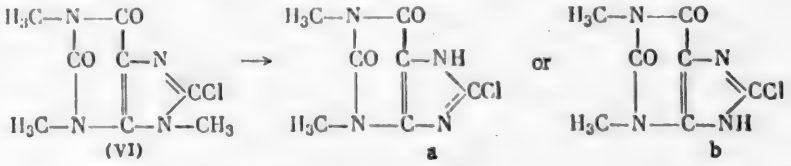
(V) (VI) (VII) (II) or (IV)

The possibility of forming 8-chloroisocaffeine (VI), unknown up to the present time, by direct chlorination of isocaffeine (V) seemed doubtful at first because the literature indicates that this reaction cannot be carried out successfully [1]; a major change in the structure of the purine molecule is said to occur when chlorine is reacted with methylated derivatives of 9-methylisoxanthine even at room temperature, and one of them is transformed into the corresponding 4-chloro-$\Delta^{5,7}$-isouric acid. Nevertheless, in spite of these statements, conditions were found for preparing 8-chloroisocaffeine (VI) in a satisfactory yield by chlorinating isocaffeine (V) with molecular chlorine in hot acetic acid.

Reduction of the resulting chlorinated compound to form the starting material (V) was conclusive evidence that the action of chlorine on (V) under these conditions was not accompanied by reactions such as those described in the above reference.

If the chlorination of (VI) results in the substitution of the hydrogen of one methyl group in the pyrimidine ring with chlorine, this would be the preferred route for preparing one of the two possible 8-chlorodimethylisoxanthines (II or IV) and also the dimethylisoxanthines (I or III), because its simplicity would give it an advantage over other methods [1], especially as the starting material, isocaffeine, is now readily available; also it can be synthesized easily by the following scheme: uric acid → 8-methylisocaffeine → isocaffeine, with good yields in all stages [2, 3].

If, as in the analogous case of 8-chlorocaffeine ($\Delta^{8,9}$), a second atom of chlorine replaces a hydrogen atom in the methyl group of the imidazole ring [4], i.e., in the present case in position 9, it would be expected that demethylation would give theophylline (1, 3-dimethylxanthine with $\Delta^{8,9}$, formula a), and not 1,3-dimethylisoxanthine, because the predominance of the stable tautomeric form with $\Delta^{7,8}$ (formula b) seemed rather improbable with an unsubstituted mobile hydrogen atom present in the imidazole ring.



(VI) a b

At first glance the results obtained seemed to confirm the similarity in behavior of isocaffeine and caffeine. The properties of (VI) and 8-chlorocaffeine [5] were similar, as were also their conversion into the dichlorides and the hydrolysis of the latter; and the substance $C_7H_7O_2N_4Cl$ formed by hydrolysis of the dichloride of (V) was indistinguishable in regard to melting point, external form and properties from 8-chlorotheophylline synthesized for comparison according to the scheme: caffeine → 8-chlorocaffeine → 8-chloro-7-chloromethyltheophylline → 8-chlorotheophylline [6, 4]. Nevertheless a mixed melting point test on this substance and 8-chlorotheophylline showed a marked depression, and visual comparison of their ultraviolet spectra showed that they were different compounds.

The substances obtained from them by reductive dehalogenation also appeared different, although they had the same composition $C_7H_8O_2N_4$. While theophylline with m.p. 268-272° and solubility of 1 : 7 in water at 100° is formed by reduction of 8-chlorotheophylline [6], the crystals obtained by demethylation and dehalogenation of 8-chloroisocaffeine melted at 352-353° and had a solubility of 1 : 80 in water at 100°.

Apparently, in the process of demethylation of 8-chloroisocaffeine (VI), as distinct from the analogous demethylation of 8-chlorocaffeine with $\Delta^{8,9}$, a methyl group splits off from the pyrimidine and not from the imidazole part of the molecule; the compounds formed in the reaction described above must therefore have been derivatives of isoxanthine with $\Delta^{7,8}$ and with the methyl group retained at N_9.

However, before this conclusion could be made definitely the possibility had to be excluded of a more profound change in the structure of the isoxanthine molecule, as a result of chlorination of 8-chloroisocaffeine (VI) under rather severe conditions (heating with a solution of chlorine in phosphorus oxychloride at 100°) and subsequent hydrolysis of the resulting dichloride.

In order to be satisfied that the substances obtained by demethylation of isocaffeine retained the isoxanthine skeleton, they were methylated under mild conditions. The formation of the original substances (V) and (VI) by methylation with diazomethane in ether solution showed that transformations similar to those described in the literature [1] did not take place in this case.

Thus, there was considerable experimental evidence that by demethylation of (VI) 8-chlorodimethylisoxanthine (II) or (IV) were obtained, and from these—dimethylisoxanthine (I) or (III).

Additional confirmation of this was found by comparing the ultraviolet spectra of the compounds obtained with the ultraviolet spectra of 8-chloroisocaffeine and isocaffeine on the one hand, and with the spectra of 8-chlorotheophylline, theophylline, 8-chlorocaffeine and caffeine on the other. The spectra of the entire isoxanthine group of compounds (Figs. 1 and 2) are almost indistinguishable from each other and are characterized by a maximum in the region of 240 mμ, which is absent in the ultraviolet spectra of all the listed derivatives of xanthine with $\Delta^{8,9}$.

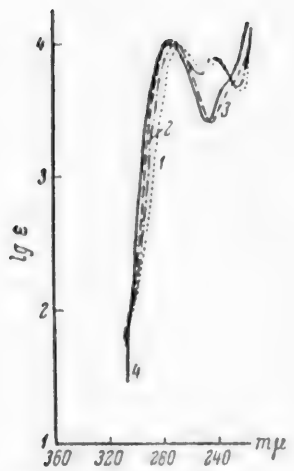


Fig. 1. Ultraviolet spectra. 1) Dimethylisoxanthine; 2) isocaffeine; 3) theophylline; 4) caffeine.

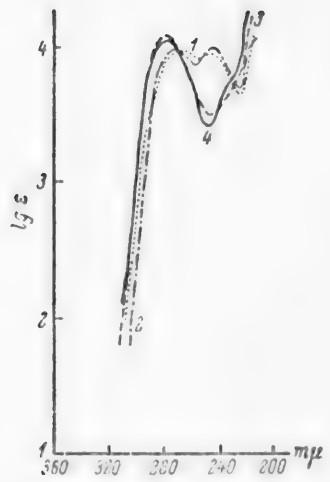


Fig. 2. Ultraviolet spectra. 1) 8-Chlorodimethylisoxanthine; 2) 8-chloroisocaffeine; 3) 8-chlorotheophylline; 4) 8-chlorocaffeine.

The question of the position of the methyl group in the pyrimidine ring of the two substances remained unanswered. The melting point of the dimethylisoxanthine formed by dehalogenation of the chloro derivative of dimethylisoxanthine coincided almost exactly with the melting point given for 1,9-dimethylisoxanthine synthesized from methylaminobarbituric acid and methylthioisocyanate [1] (350°), while 3,9-dimethylisoxanthine, according to the data of these authors, decomposes at 364°. Thus, comparison of the melting point of the compound formed by reduction of chlorodimethylisoxanthine with the literature data indicated that in the above-described demethylation of isocaffeine, the N_3 methyl group was split off from the pyrimidine part of the molecule, and that the compounds obtained were 1,9-dimethyl-3-chloromethyl-8-chloroisoxanthine, 8-chloro-1,9-dimethylisoxanthine (II) and 1,9-dimethylisoxanthine (I). •

EXPERIMENTAL

8-Chloroisocaffeine [8-chloro-1,3,9-trimethylisoxanthine (VI)]. 100 g sample of the material (V) [2], dried at 120°, was dissolved in 300 ml of glacial acetic acid at 80-90° and 70 g of dry chlorine was passed into the stirred solution during one hour. The temperature of the mixture rose to 110° and a finely crystalline solid (VI) separated. The hot mixture was filtered and the solid was washed with hot acetic acid and alcohol; 84.1 g (71.6%) of material (VI) was obtained melting at 260-261° (dec.). After crystallization from water it melted at 261-262° without decomposition. From the cooled acetic acid filtrate a solid (8-10 g) separated with a melting range of 250-258° (dec.); it was washed with 20 ml of boiling water and then crystallized from water. The total yield of crystalline 8-chloroisocaffeine (VI) was 72.6 g (61.8%). Fine white needles, almost insoluble in cold water and organic solvents; solubility in boiling water 1 : 40, in boiling alcohol 1 : 100.

Found %: Cl 15.06; C 42.18; H 3.93. $C_8H_9O_2N_4Cl$. Calculated %: Cl 15.53; C 42.10; H 3.95.

Dehalogenation of 8-chloroisocaffeine. a) To a stirred mixture of 1.1 g of chloroisocaffeine, 1 g of red phosphorus and 10 ml of acetic anhydride was added 7 ml of 50% HI in the course of 15 min and the mixture boiled for one hour. From the cooled filtered solution water was distilled off under vacuum, and traces of HI were distilled off twice with water. The residue was dissolved in 10 ml of water, and the solution was neutralized with NH_4OH to pH 7, heated with charcoal and filtered. After cooling, 0.4 g of long, thin, white needles of isocaffeine (V) separated; solubility in boiling water 1 : 2, m.p. 260-263°. A mixture with isocaffeine melted at 260-263°. After crystallizing from water the m.p. was 280-282°.

• The experimental investigation of the structure of these compounds will be described in a later communication.

b) A solution of 0.5 g of 8-chloroisocaffeine (VI) in 1.5 ml of water was boiled with 2 g of Raney nickel and 2.2 ml of 0.1 N NaOH for 2 hr. The solution was filtered and concentrated under vacuum to a volume of 1-1.5 ml; after cooling 0.15 g of small white needles of isocaffeine (V) separated with m.p. of 269-270°. A mixture with isocaffeine melted at 269-270°.

1,9-Dimethyl-3-chloromethyl-8-chloroisoxanthine. A 15 g sample of dry, powdered chloroisocaffeine (VI) was heated with a solution of 6 g of chlorine in 45 ml of $POCl_3$ in a sealed tube at 95-100° for 24-25 hr. The external appearance of the reaction mixture changed and large crystals separated. These were filtered off and washed with ether; weight 13.8 g, m.p. 198-200°. After crystallization from methylethylketone (1 : 30) or large volumes of ethyl acetate the product melted at 203.5-205°.

Found %: Cl 27.33; C 36.49; H 3.20. $C_8H_8O_2N_4Cl_2$. Calculated %: Cl 27.00; C 36.50; H 3.04.

1,9-Dimethyl-8-chloroisoxanthine (II). a) A sample of purified 1,9-dimethyl-3-chloromethyl-8-chloroisoxanthine weighing exactly 4.4650 g was boiled under reflux with 200 ml of water for three hours. The odor of formaldehyde was observed and a solid separated. After cooling the solid was filtered off, washed with water and dried. Weight of (II) 2.883 g (80%), m.p. 305-307°. For analysis it was crystallized from water (1 : 200) or 96% alcohol; m.p. 318° (dec.). A mixture with 8-chlorotheophylline (m.p. 305° [4]) melted at 280-290°.

Found %: Cl 16.84, 16.73. $C_7H_7O_2N_4Cl$. Calculated %: Cl 16.55.

The aqueous filtrate after separation of 1,9-dimethyl-8-chloroisoxanthine was neutralized (methyl orange indicator) with 16.64 ml of 1 N NaOH (the calculated quantity of NaOH required was 16.89 ml).

b) A 15 g sample of (VI) and a solution of 6.4 g of chlorine in 50 ml of $POCl_3$ were heated on a steam-bath for 24 hr. The solid obtained (14 g) was boiled with 400 ml of water for 3 hr, then cooled and filtered; yield of 1,9-dimethyl-8-chloroisoxanthine was 8.14 g (58%), m.p. 305-307°.

The sodium salt of 1,9-dimethyl-8-chloroisoxanthine crystallized from water (1 : 7) as short, thick needles; solubility in boiling anhydrous alcohol 1 : 70.

Found %: N 23.85, 23.71. $C_7H_6O_2N_4ClNa$. Calculated %: N 23.67.

8-Chloroisocaffeine (VI) from 8-chlorodimethylisoxanthine (II). To a suspension of 1 g of 8-chlorodimethylisoxanthine (II) in 1 liter of dry ether was added an ether solution of 2-2.3 g of CH_2N_2, the reaction mixture being cooled with ice, after which it was allowed to stand 4 days at 20°. The solid was filtered by suction and washed with ether. Weight of material was 0.8 g, m.p. 239-246°. After crystallization from 30 ml of water the yield of 8-chloroisocaffeine (VI) was 0.55 g (52%), m.p. 252-255°. A mixture with (VI) melted at 255-257°.

1,9-Dimethylisoxanthine (I). A volume of 7 ml of 50% HI was added in the course of 15 min to a mixture of 8-chlorodimethylisoxanthine (II), 1 g of red phosphorus and 10 ml of acetic anhydride, and the mixture boiled 1 hr. It was then cooled and filtered, the water distilled off under vacuum and traces of HI distilled off twice with water. The residue was dissolved in 5 ml of water, filtered and neutralized with NH_4OH to pH 3. Weight of material obtained was 0.85 g, m.p. 270-280°; it crystallized from 60 ml of water in the form of fine white needles; yield 0.52 g (62%), m.p. 351-352°. 1,9-Dimethylisoxanthine (I) was slightly soluble in cold water and its solubility in boiling water was 1 : 80.

When 0.1873 g of the material was dried at 120°, it lost 0.088 g in weight (4.69%), which corresponds to 0.5 mole of water.

Found %: C 46.59; H 4.52; N 30.57. $C_7H_8O_2N_4$. Calculated %: C 46.66; H 4.44; N 31.10.

The material upon standing in the air absorbed 4.7% moisture and formed a stable hemihydrate.

Found %: N 29.66; C 44.07; H 4.91. $C_7H_8O_2N_4 \cdot 0.5\ H_2O$. Calculated %: N 29.62; C 44.44; H 4.76.

Isocaffeine (V) from 1,9-dimethylisoxanthine (I). To a mixture of 2 g of (I) in 1 liter of dry ether was added an ether solution of 2-2.3 g of CH_2N_2, the reaction mixture being cooled with ice after which it was allowed to stand 4 days at room temperature. The solid after separation and washing with ether yielded 1.9 g of a mixture melting at 255-270°. It was boiled with 6 ml of water and filtered. The weight of undissolved impure starting material (I) was 0.5 g, m.p. 315-320°. The aqueous filtrate was cooled and 0.5 g of crystals

separated with m.p. 265-270°; after a second crystallization from water the m.p. was 278-281°. A mixture with isocaffeine melted at 280-282°.

SUMMARY

1. When isocaffeine (1,3,9-trimethylisoxanthine) was reacted with molecular chlorine in hot acetic acid, chlorine replaced the hydrogen in the C_8 position and 8-chloroisocaffeine was formed.

2. When 8-chloroisocaffeine (8-chloro-1,3,9-trimethylisoxanthine) was reacted with molecular chlorine in hot phosphorus oxychloride, chlorine replaced a hydrogen in a methyl group (apparently in the N_3 position) in the pyrimidine part of the molecule. Hydrolysis of the resulting dichloride caused a chloromethyl group to split off with liberation of hydrogen chloride and formaldehyde. Reductive dehalogenation of the monomethyl derivative of 8-chloro-9-methylisoxanthine thus obtained resulted in the formation of the corresponding dimethylisoxanthine which, judging by the melting point, appeared to be 1,9-dimethylisoxanthine.

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SYNTHESIS OF DERIVATIVES OF ISOXANTHINE

II. SOME AMINO-ACID DERIVATIVES OF METHYLATED XANTHINE AND ISOXANTHINE

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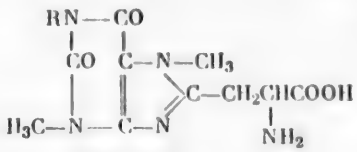
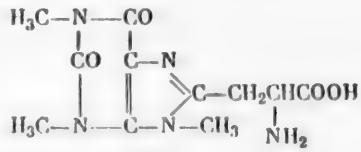
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1878-1884, June, 1960
Original article submitted June 9, 1959

The synthesis of amino-acid derivatives of xanthine ($\Delta^{8,9}$) and isoxanthine ($\Delta^{7,8}$), in which the purine part of the molecule and the amino-acid or dipeptide residues are joined by covalent bonds of different degrees of stability, was undertaken with the object of seeking new biologically active substances. The present communication deals with the preparation of derivatives of methylated xanthine and 1,3,9-trimethylisoxanthine connected through the C_8 atom with the β-carbon atom of alanine.



(I) R = CH$_3$
(II) R = H



(III)

There are two possible methods of synthesizing these compounds.

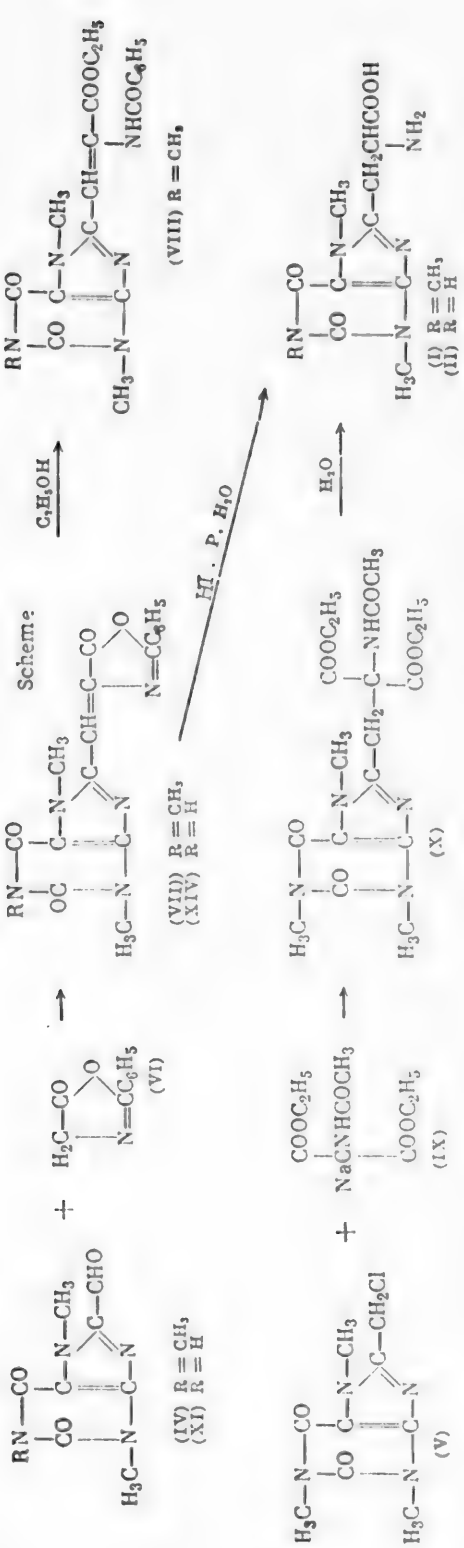
1. Condensation of methylated xanthine-(or isoxanthine)-8-aldehydes with hippuric acid followed by reduction and saponification of the resulting 2-phenyloxazolones-5, substituted in position 4 with a xanthine residue.

2. Condensation of 8-chloromethyl derivatives of N-methylated xanthine (or isoxanthine) with sodium acetylaminomalonic ester and saponification of the resulting diesters.

Both methods were investigated experimentally following the example of two compounds studied in detail—caffeine-8-aldehyde [1] (IV), described previously by one of us, and 8-chloromethylcaffeine [2, 3] (V).

The reaction with hippuric acid was carried out by the method of Galat [4], by cyclizing hippuric acid with acetic anhydride in the presence of potash and then condensing caffeine-8-aldehyde (IV) with the 2-phenyloxazolone-5 (VI) formed by cyclization. The 4-[(caffeine-8)-methylene]-phenyloxazolone-5 (VII) formed in the reaction was transformed into the ethyl ester of β-(caffeine-8)-α-benzoylaminoacrylic acid (VIII) for identification. Reduction of the oxazolone (VII) with HI in the presence of red phosphorus, and hydrolysis, gave β-(caffeine-8)-alanine (I).

A higher yield of (I) was attained with the second method, viz. by condensation of 8-(chloromethyl)-caffeine (V) with sodium acetylaminomalonic ester (IX) in anhydrous alcohol and subsequent hydrolysis of the condensation product (X) with 20% hydrochloric acid (see scheme).



Scheme

Suitable starting materials for the synthesis of β-(theobromine-8)-alanine (II), which is distinguished from β-(caffeine-8)-alanine (I) by the presence of an unsubstituted hydrogen on a nitrogen of the pyrimidine part of the molecule, would be 8-(monochloromethyl)-theobromine or theobromine-8-aldehyde (XI), which could be obtained from 8-(dichloromethyl)-theobromine (XIII). None of these compounds was known previous to the present study, the only chloro derivative of 8-methyltheobromine (XII) described in the literature being 8-(trichloromethyl)-theobromine [5, 6], which is an intermediate in the synthesis of theobromine, based on the demethylation of 8-methyltheobromine [6, 2]. Therefore the problem arose of preparing 8-mono- or 8-(dichloromethyl)-theobromine and their hydrolysis products as the first step in the synthesis of β-(theobromine-8)-alanine.

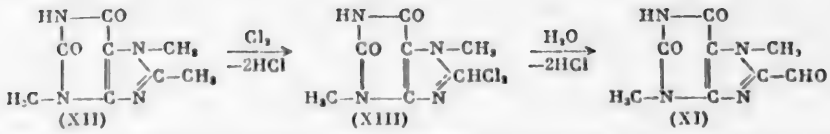
As a result of a study of the chlorination of (XII), undertaken in connection with this problem, conditions were found for preparing a mixture of the di- and trichloro-derivatives of 8-methyltheobromine, which contained a predominating proportion of the first (i.e., XIII), and which was comparatively easy to separate by means of the different solubilities of these two compounds in ethyl acetate or benzene. The dichloro (XIII) after separation was transformed into the aldehyde (XI) by boiling it with water.

Condensation of theobromine-8-aldehyde (XI) with 2-phenyloxazolone-5 (VI), and also the reduction and hydrolysis of the intermediate 4-[(theobromine-8)-methylene]-2-phenyloxazolone-5 (XIV) proceeded completely analogously to the reactions mentioned above and thus provided a method of preparing β-(theobromine-8)-alanine (II).

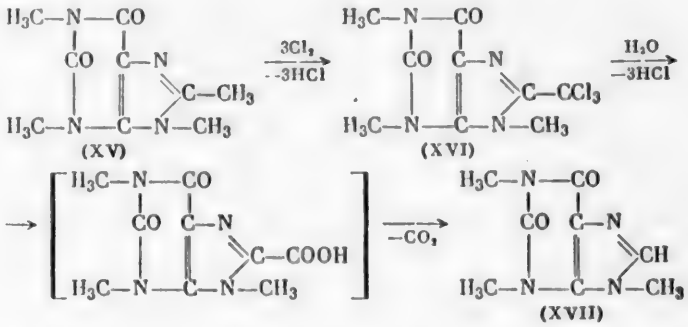
Amino-acid derivatives of isoxanthine ($\Delta^{7,8}$) were particularly interesting as possible antimetabolites of the purine series, i.e., compounds analogous with respect to the position of the double bond in the imidazole part of the purine molecule to the purine bases, which are a constituent part of the purine nucleosides.

Synthesis of methylated β-(isoxanthine-8)-alanine likewise required a study of the chlorination of methylisocaffeine (XV), which at the present time is readily available for synthetic purposes [7]; its 8-chloro derivative (mono- or di-), by analogy with the above described synthesis of methylated derivatives of β-(xanthine-8)-alanine, was chosen as the starting material for the synthesis of β-(isocaffeine-8)-alanine (III).

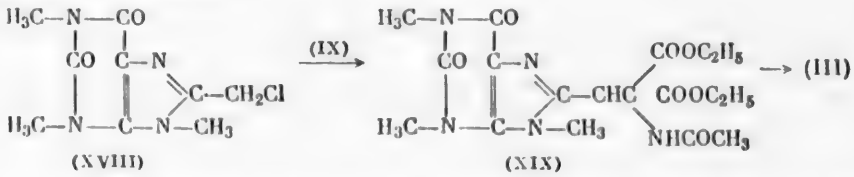
When methylisocaffeine was chlorinated under different conditions it was observed that substitution of all three hydrogens of the C_8 methyl group could be effected very easily under conditions essentially the same as for the preparation of 8-trichloromethylcaffeine, i.e., in chlorobenzene with the calculated quantity of chlorine at a temperature above the decomposition temperature of the



chlorine adduct [8]. The 8-trichloromethylisocaffeine (XVI) thus formed readily underwent alcoholysis when heated with alcohol and was transformed into the ester of isocaffeine-8-carboxylic acid or was hydrolyzed quantitatively by heating with water, in which case the unstable isocaffeine-8-carboxylic acid immediately decarboxylated. Thus, isocaffeine (XVII) was readily prepared from methylisocaffeine, and therefore the problem was solved of synthesizing isocaffeine, which has been difficult to obtain up to the present time, by a comparatively short, simple method with a good yield.



Partial substitution of the hydrogens of the methyl group in position 8 of (XV) on the other hand was very different. Regardless of the chlorinating conditions the reaction mass was always a mixture of (XVI) with a hydrochloride of the initial methylisocaffeine (XV), from which it was impossible to separate the intermediate chlorinated (mono- or di-) derivatives of methylisocaffeine as individual compounds. Therefore 8-(monochloromethyl)-isocaffeine (XVIII) had to be synthesized by an indirect route, viz. from 8-chloroisocaffeine [9] through the preparation of (isocaffeine-8)-malonic ester and then 8-hydroxymethylisocaffeine. The condensation of (XVIII) with sodium acetylaminomalonic ester (IX) took place very vigorously; the reaction was finished within 20-30 min and thus provided a method of preparing 8-(isocaffeine-8)-alanine (III) in a 40.5% yield based on the initial 8-(chloromethyl)-isocaffeine.



All three derivatives of alanine (I, II and III) were crystalline substances, very slightly soluble in water, and they gave a blue-violet coloration characteristic of amino acids when boiled with a solution of ninhydrin.

EXPERIMENTAL

8-(Dichloromethyl)-theobromine (XIII). To a boiling suspension of 20 g of methyltheobromine (XII) in 250 ml of dry chlorobenzene was added 15 g of chlorine (1 hr). The chlorobenzene was distilled off under vacuum, and the residue was extracted with hot ethyl acetate or benzene. Undissolved original material (XII) weighed 5.35 g, m.p. 294.5-295.5°. Upon cooling the solutions 9.78 g of 8-(dichloromethyl)-theobromine (XIII) with m.p. 234-237° separated out. From the filtrates 3.95 g of impure 8-(trichloromethyl)-theobromine with m.p. 172-198° separated out. 8-(Dichloromethyl)-theobromine is a white crystalline substance with m.p. 240.5-241.5°. It crystallized from ethyl acetate (1 : 140), alcohol (1 : 80), benzene (1 : 120), or chloroform (1 : 150).

Found %: Cl 26.17, 26.06; N 20.79, 21.01. $C_8H_8O_2N_4Cl_2$. Calculated %: Cl 27.00; N 21.29.

Theobromine-8-aldehyde (XI). A 17 g sample of 8-(dichloromethyl)-theobromine (XIII) was boiled with 270 ml of water for 4 hr, cooled, filtered, and the solid washed with water. Yield of (XI) was 9.9 g (76%).

m.p. 280-282°. The filtrate was concentrated to one third of its volume, and 0.8 g more of theobromine-8-aldehyde with m.p. 267-270° separated. For analysis it was crystallized twice from water; m.p. 288-290° (dec.).

Found %: C 46.21; H 3.72; N 27.20. $C_8H_8O_3N_4$. Calculated %: C 46.15; H 3.84; N 26.92.

Theobromine-8-aldehyde (XI) formed fine white needles; it crystallized from water (1 : 70), ethyl acetate (1 : 50), chlorobenzene, benzene, and anhydrous alcohol. It was only slightly soluble in boiling CCl_4. It gave qualitative reactions characteristic of aldehydes. With an alcoholic solution of 2,4-dinitrophenylhydrazine it formed a red crystalline precipitate melting at 330-331°. With an aqueous solution hydroxylamine hydrochloride in the presence of CH_3COONa it formed a white precipitate melting at > 341°. The 2,4-dinitrophenylhydrazone and the oxime could not be purified for analysis because they were practically insoluble.

Theobromine-8-aldehyde anil. A solution containing 1 g of (XI) and 0.5 g of aniline in 100 ml of alcohol was boiled for 1 hr, filtered by suction, and the crystals washed with hot alcohol. Yield 0.43 g (31.6%); m.p. 283.5-283.8° (from alcohol).

Found %: N 24.35. $C_{14}H_{13}O_2N_5$. Calculated %: N 24.73.

Isocaffeine (1,3,9-Trimethylisoxanthine) (XVII) from Methylisocaffeine (XV)

1. 8-(Trichloromethyl)-isocaffeine (XVI). A suspension of 200 g of (XV) in 2200 ml of dry chlorobenzene was heated (90-100°) and 240 g of chlorine introduced with stirring.* All the solid gradually went into solution. The reaction mass crystallized on cooling, and the precipitate was filtered off and washed with 100 ml of chlorobenzene. The weight of (XVI) was 200 g, and the m.p. 203-205°. Part of the chlorobenzene was distilled from the filtrate under vacuum (to a residual volume of 300-400 ml), and after cooling 60 g more of (XVI) with m.p. 198-200° separated out. For analysis it was crystallized from benzene (1 : 50), m.p. 214.5-215° (dec.).

Found %: C 34.70; H 2.91; Cl 33.81. $C_9H_9O_2N_4Cl_3$. Calculated %: C 34.67; H 2.88; Cl 34.12.

8-(Trichloromethyl)-isocaffeine was a crystalline substance, soluble in hot ethyl acetate (1 : 70), benzene (1 : 50), chloroform (1 : 5), trichloroethylene (1 : 90), and chlorobenzene (1 : 20).

2. Isocaffeine (XVII). Two hundred grams of (XVI) with m.p. 203-205° was boiled with 600 ml of water, and after it was completely dissolved charcoal was added and the boiling continued for 1 hr. Isocaffeine (XVII) was precipitated by adding 40% NaOH to a pH of 6.7-6.8 while stirring and cooling. The precipitate was separated, washed with ice-water, and dried at 100°. Yield of (XVII) after crystallizing it from 340 ml of water was 99-100 g, and m.p. 285-286°.

Found %: N 28.55. $C_8H_{10}O_2N_4$. Calculated %: N 28.83.

By heating 60 g of material melting at 198-200°, which separated from the chlorobenzene filtrate, with 120 ml of water, an additional 11 g of (XVII) with m.p. 277-277.5° was obtained. The total yield of (XVII) was 110-111 g [64.5% on the starting material (XV), i.e., for both steps].

Ethyl ester of isocaffeine-8-carboxylic acid. A 2 g sample of 8-(trichloromethyl)-isocaffeine (XVI) was boiled with 10 ml of alcohol for 2 hr. After cooling, 1.66 g of impure ester separated out. After several crystallizations from alcohol, the product melted at 261.5-262°.

Found %: N 20.79, 20.75. $C_{11}H_{14}O_4N_4$. Calculated %: N 21.03.

β-(Caffeine-8)-alanine (I)

1. 2-Phenyl-4-[(caffeine-8)-methylene]oxazolone-5 (VII). A 4.7 g sample of hippuric acid was mixed with 1.7 g of K_2CO_3 and 20 ml of acetic anhydride, and after the hippuric acid had dissolved (30-35 min) 5.5 g of (IV) was added and the mixture allowed to stand 24-30 hr. The mixture was treated with 50 ml of ice-water and filtered after 2-3 hr. The product (VII) after washing with water weighed 7.6 g (93%). For analysis it was crystallized from CH_3COOH (1 : 60), m.p. 261-262° (dec.).

Found %: C 56.10; H 4.64; N 16.26. $C_{18}H_{15}O_4N_5 \cdot CH_3COOH$. Calculated %: C 56.47; H 4.50; N 16.46.

*In order to remove traces of moisture from the reaction mass, 200-250 ml of chlorobenzene was previously distilled off (to give a clear distillate and a vapor temperature of 130°).

Ethyl ester of α-benzoylamino-β-(caffeine-8)-acrylic acid (VIII). To 0.7 g of (VII) was added 50 ml of anhydrous ethanol containing a catalytic quantity of C_2H_5ONa. The weight of precipitate, filtered off after 12 hr, was 0.7 g melting at 242-245°. For analysis it was crystallized from 400 ml of alcohol, m.p. 256-258°.

Found %: C 58.65; H 5.15; N 16.85. $C_{20}H_{21}O_5N_5$. Calculated %: C 58.38; H 5.14; N 17.01.

β-(Caffeine-8)-alanine (I). To a mixture of 3.6 g of the substance (VII), 2 g of dry red phosphorus and 12.5 ml of acetic anhydride was added 13 ml of freshly distilled 49% HI dropwise with stirring. The reaction mixture was boiled 4 hr, cooled, filtered and the filtrate evaporated to dryness under vacuum. The residue was dissolved in 30-40 ml of water and the solution was washed several times with ether. The water was distilled off again under vacuum, and traces of HI were distilled off twice with water under vacuum. The residue was dissolved in 100 ml of alcohol, and the solution was cooled, neutralized with $(C_2H_5)_3N$ to pH 7, and filtered after 12 hr. The precipitate (I) was crystallized twice from water. The yield was 1 g (33%), m.p. 275-277° (dec.).

A 0.8289 g sample of (I) lost 0.0495 g in weight when dried at 120 °, i.e., 5.97%, which corresponds to 1 mole of water of crystallization.

Found %: C 44.06; H 5.74; N 23.77. $C_{11}H_{15}O_4N_5 \cdot H_2O$. Calculated %: C 44.15; H 5.68; N 23.40.

2. Diethyl ester of (caffeine-8-methyl)-acetylaminomalonic acid (X). To a solution of 0.74 g of Na in 60 ml of alcohol was added 7.03 g of acetylaminomalonic ester, and after boiling for 30 min, 7.3 g of 8-chloromethylcaffeine (V) was introduced and the mixture heated while stirring for 1.5-2 hr longer until the alkaline reaction to phenolphthalein disappeared. The precipitate was filtered off and washed with water; its weight was 9.82 g, m.p. 204-206°. For analysis it was crystallized twice from alcohol, m.p. 214-215°.

Found %: N 16.27. $C_{18}H_{25}O_7N_5$. Calculated %: N 16.55.

β-(Caffeine-8)-alanine (I). A mixture of 9 g of the impure ester (X) and 100 ml of 20% HCl was boiled for 6 hr. The acidic solution was evaporated to dryness under vacuum, traces of acid were distilled off twice with water, and the residue was dissolved in 30 ml of water and neutralized with $(C_2H_5)_3N$ to pH 7. After 24 hr the precipitate was filtered by suction and crystallized from 50 ml of water. A weight of 3.82 g (60%) of (I) was obtained melting at 270-275° (dec.).

2-Phenyl-4-[(theobromine-8)-methylene]oxazolone-5 (XIV). A mixture of 4.72 g of hippuric acid, 1.7 g of K_2CO_3 and 20 ml of acetic anhydride was prepared, after 30 min 5 g of (XI) was added, and the mixture was allowed to stand until the next day. It was mixed with 50 ml of ice-water and filtered after two hr; the solid was washed with water. The yield of (XIV) was 6.62 g (78%), m.p. 295-297° (dec.). For analysis it was crystallized from CH_3COOH, m.p. 301-302° (dec.).

Found %: N 17.32. $C_{17}H_{13}O_4N_5 \cdot CH_3COOH$. Calculated %: N 17.01.

β-(Theobromine-8)-alanine (II). The preparation of this compound was similar to that of (I). From 4.8 g of (XIV), 2.7 g of red phosphorus, 17 ml of acetic anhydride and 17.5 ml of 49% HI was obtained 3.25 g of crude (II) melting at 246-249° (dec.). The yield after crystallization from 50 ml of water was 1.7 g (47%), m.p. 282-284° (dec.).

Found %: C 45.39; H 5.06; N 25.87. $C_{10}H_{13}O_4N_5$. Calculated %: C 44.94; H 4.90; N 26.19.

Diethyl ester of (isocaffeine-8-methyl)-acetylaminomalonic acid (XIX). To a solution of sodium acetylaminomalonic ester (IX) (from 4.5 g acetylaminomalonic ester and 0.46 g of Na) in 20 ml of anhydrous alcohol was added 6.6 g of (XVIII), the reaction mixture was boiled for 1 hr and then mixed with 50 ml of water; 6.6 g of acid (XIX) with m.p. 219-221° precipitated. When the filtrate was evaporated and treated with water 1.3 g more of (XIX) precipitated. The total yield was 7.9 g (89%). For analysis it was crystallized from alcohol, m.p. 222-224°.

Found %: N 16.52. $C_{18}H_{25}O_7N_5$. Calculated %: N 16.55.

β-(Isocaffeine-8)-alanine (III). A sample of (XIX) weighing 6.6 g was boiled with 100 ml of 20% HCl for 6 hr. The acid was distilled off (traces of acid were distilled off with water), the residue was dissolved in 20 ml of water and neutralized with $(C_2H_5)_3N$, and 75 ml of alcohol was added. The weight of crude (III) was 2.8 g. The yield after two crystallizations from water (1 : 4) was 2.1 g (45.5%), m.p. 254-256° (dec.).

Found %: C 43.94; H 5.69; N 23.18. $C_{11}H_{15}O_4N_5 \cdot H_2O$. Calculated %: C 44.15; H 5.68; N 23.40.

SUMMARY

1. β-(3,7-Dimethylxanthine-8)-alanine, β-(1,3,7-trimethylxanthine-8)-alanine and β-(1,3,9-trimethylisoxanthine-8)-alanine were synthesized by two methods: a) Condensation of methylated xanthine-8-aldehydes and 2-phenyloxazolones-5 followed by reduction and hydrolysis of the condensation products; b) condensation of 8-chloromethyl derivatives of methylated xanthine and isoxanthine with sodium acetylaminomalonic ester followed by saponification of the condensation product.

2. Theobromine-8-aldehyde was synthesized by chlorination of 8-methyltheobromine and hydrolysis of the resulting 8-(dichloromethyl)-theobromine.

3. A convenient method of synthesizing isocaffeine was developed, based upon chlorination of methylisocaffeine and hydrolysis of the resulting 8-(trichloromethyl)-isocaffeine.

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SYNTHESIS OF 3- AND 4-HYDROXYPIPERIDINE DERIVATIVES

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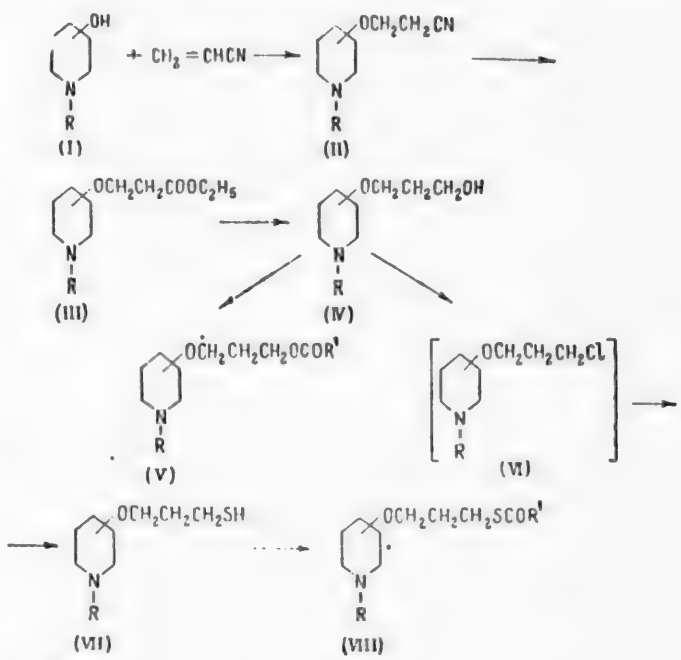
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1885-1893,
June, 1960
Original article submitted June 26, 1959

In a previous communication we described the synthesis of complex esters of 3-hydroxyquinuclidine and 3-[γ-hydroxy(thio)-propyloxy]-quinuclidines [1]. During pharmacological investigation of these compounds it was observed that some of them show high cholinomimetic activity. It appeared of interest to study the pharmacological properties of esters of 1-alkyl-3(4)-hydroxypiperidines, and also of 3(4)-[γ-hydroxy(thio)-propyloxy]-piperidines, closely related structurally to the corresponding quinuclidine derivatives.

1-Ethyl-3-hydroxypiperidine, derived from furfural [2], and 1-ethyl(methyl)-4-hydroxypiperidines, derived from β,β-dicyanodiethylamine [3, 4], were necessary for this work. In the latter case, the piperidones-4 formed as intermediates were reduced by us with sodium borohydride, instead of sintered nickel catalyst as indicated in the literature. Esterification was accomplished by heating the hydroxypiperidines with the acid chlorides of the acids in benzene solution.

1-Alkyl-3(4)-[γ-hydroxy(thio)-propyloxy]-piperidines were synthesized according to the following scheme:

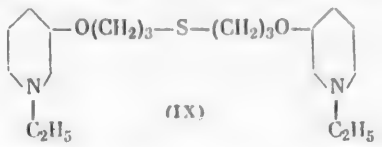


R = CH_3, C_2H_5.

R' = CH_3, C_6H_5, NOC_6H_4, $(C_6H_5)_2CH$ etc.

1-Alkyl-3(4)-hydroxypiperidines (I) readily combine with acrylonitrile when the reaction is carried out in absolute dioxane in the presence of a methanol solution of caustic potash. The 1-alkyl-3(4)-[β-cyanoethyloxy]-piperidines (II) formed undergo alcoholysis on prolonged heating with alcohol in the presence of concentrated sulfuric acid or on bubbling a stream of dry hydrogen chloride into a boiling alcoholic solution of the nitrile. The 1-alkyl-3(4)-[β-carbethoxyethyloxy]-piperidines obtained are reduced with lithium alumohydride to 1-alkyl-3(4)-[γ-hydroxypropyloxy]-piperidines (IV), which on heating with the acid chlorides of acids in benzene solution form esters (V).

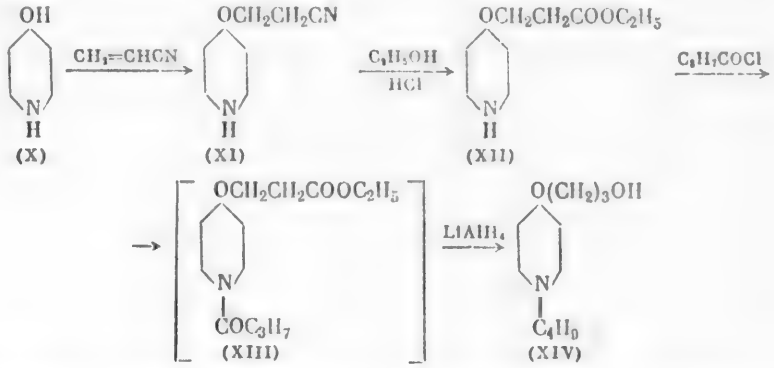
In the synthesis of mercaptoalkyloxypiperidines (VII) the corresponding hydroxyderivatives (IV) were converted into chlorides (VI) which were reacted with thiourea without purification of the hydrochlorides; the thiourea salts occurring as intermediates were decomposed on heating with caustic soda, 1-alkyl-3(4)-[γ-mercaptopropyloxy]-piperidines (VII) being formed. It should be noted that on reacting the base 1-ethyl-3-(γ-chloropropyloxy)-piperidine with thiourea and on subsequent treatment of the reaction products with caustic soda the corresponding mercaptan is not formed, but instead di-[γ-(1-ethylpiperidine-3-oxy)-propyl]-sulfide (IX).



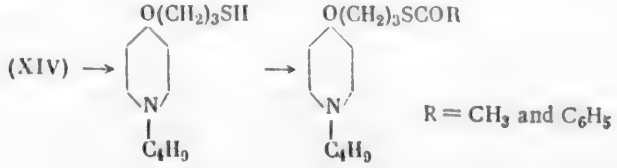
(IX)

Thioesters (VIII) were obtained by reacting mercaptans (VII) with the acid chlorides of acids in ethereal solution.

Synthesis of similar derivatives of 1-butyl-4-hydroxypiperidine was achieved by a somewhat different method. The latter, according to the literature available, is formed by conversion of 1-butyl-β,β-dicyanodiethylamine into 1-butylpiperidone-4 and then into 1-butyl-4-hydroxypiperidine [4]. However, we were not successful in obtaining original 1-butyl-β,β-dicyanodiethylamine by the method described in the literature—butylation of β,β-dicyanodiethylamine with butyl iodide and bromide in the presence of anhydrous sodium bicarbonate in an alcoholic medium [3]. Accordingly, 1-butyl-4-(γ-hydroxypropyloxy)-piperidine synthesis was undertaken in a different manner, omitting formation of 1-butyl-4-hydroxypiperidine.



4-Hydroxypiperidine (X), obtained by reduction of the hydrochloride of piperidone-4 with sodium borohydride, combines with acrylonitrile, under the conditions described above, through the hydroxy group only. The 4-(β-cyanoethyloxy)-piperidine (XI) so obtained is converted by alcoholysis into 4-(β-carbethoxyethyloxy)-piperidine (XII), which on reacting with the acid chloride of butyric acid forms 1-butyroyl-4-(β-carbethoxyethyloxy)-piperidine (XIII). Owing to the fact that this substance decomposes on distillation, it was reduced directly with lithium alumohydride to 1-butyl-4-(γ-hydroxypropyloxy)-piperidine (XIV). From compound (XIV) by the method described above was obtained 1-butyl-4-(γ-thiopropyloxy)-piperidine, which was converted into the acetic and benzoic esters.



R = CH_3 and C_6H_5

TABLE 1

Preparation No.	R	Melting point of hydrochloride	Yield (%)	Empirical formula	% N		% Cl	
					found	calc.	found	calc.
1	CH_3	179—181°	93.2	$C_9H_{17}O_2N \cdot HCl$	6.53	6.75	17.09	17.11
2	C_2H_5	174—175	78.7	$C_{10}H_{19}O_2N \cdot HCl$	6.39	6.32	15.98	16.03
3	$NO_2C_6H_4$	175—177	82	$C_{14}H_{18}O_4N_2 \cdot HCl$	8.84	8.90	11.34	11.27
4	$C_6H_5OCH_2$	160—162	68.6	$C_{14}H_{21}O_3N \cdot HCl$	4.97	4.67	11.84	11.85
5	$C_6H_5CH{=}CH$	164—166	90.6	$C_{16}H_{21}O_2N \cdot HCl$	4.65	4.74	11.97	12.01

During pharmacological investigation of the preparations, it was observed that the esters of 1-alkyl-3-hydroxypiperidine and 1-alkyl-4-[γ-hydroxy(thio)-propyloxy]-piperidine possess slight peripheral cholinolytic activity.

EXPERIMENTAL

1-Ethyl-3-[(p-chlorobenzoyl)-oxy]-piperidine. A mixture of 1.4 g of 1-ethyl-3-hydroxypiperidine, 2.5 g of the acid chloride of p-chlorobenzoic acid, and 15 ml of absolute benzene were boiled for 8 hr. The reaction product was diluted with 20 ml of absolute ether and the precipitate filtered off. 2.15 g (62.5%) of the hydrochloride of the ester was obtained, consisting of colorless crystals, readily soluble in water and alcohol, sparingly in acetone.

M.p. 185-187°C (from an alcohol-acetone mixture).

Found %: N 4.66; Cl 21.90. $C_{14}H_{18}O_2NCl \cdot HCl$. Calculated %: N 4.42; Cl 21.72.

Physical constants and results of analyses of esters of 1-ethyl-3-hydroxypiperidine obtained similarly are shown in Table 1.

4-Hydroxypiperidine. To a solution of 3.5 g of piperidone-4 hydrochloride in 30 ml of alcohol was added 3.5 g of sodium borohydride with stirring for 2 hr. The reaction product was cooled with ice water so that the temperature of the mixture did not rise above 25° during addition of sodium borohydride. After standing for 20 hr at room temperature, 7 ml of water was added and the solution evaporated in vacuo. The residue was dissolved in 30 ml of water, extracted with benzene, the benzene solution dried with potash, evaporated in vacuo, and the residue distilled. 1.6 g (61%) of 4-hydroxypiperidine was obtained. B.p. 106° (13 mm).••

1-Methyl-4-hydroxypiperidine. 29.5 g of 1-methyl-piperidone-4 was reduced with 12 g of sodium borohydride in 200 ml of methyl alcohol. The reaction was carried out in a manner similar to that described above Yield, 25 g (83.5%). B.p. 94° (12 mm). •••

1-Ethyl-4-hydroxypiperidine. By reducing 12.8 g of 1-ethylpiperidone-4 with 4 g of sodium borohydride in 100 ml of methyl alcohol, 10.9 g (84.5%) of 1-ethyl-4-hydroxypiperidine was obtained. B.p. 91° (5 mm).••••

1-Ethyl-3-(β-cyanoethyloxy)-piperidine. To a solution of 20 g of 1-ethyl-3-hydroxypiperidine in 100 ml of absolute dioxane was added 3.2 ml of a 30% caustic potash solution in methyl alcohol, and then 32 ml of acrylonitrile with stirring for 20 min. The reaction mixture was heated at 60-65° for 4 hr and evaporated in vacuo. The residue was dissolved in 45 ml of 17% hydrochloric acid, the hydrochloric solution extracted with ether in order to remove substances of a neutral character, then treated with a 50% potash solution, and 1-ethyl-3-(β-cyanoethyloxy)-piperidine extracted with ether. The ethereal solution was dried with potash, evaporated

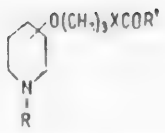
•Carried out in the pharmocology department of VNIKhFI by K. A. Zaitseva and T. K. Trubitsina under the direction of M. D. Mashkovskii.

••A b.p. of 211-212° (745 mm) is indicated in the literature [5].

•••95-98° (16 mm) [4].

•••• According to the data in the literature [6]: b.p. 102-103° (15 mm).

TABLE 2

Properties of Ester of General Formula 

Sample No.	R	X	R'	Temperature		Yield (in %)
				b.p. (pressure in mm)	m.p. of hydrochloride	
						3 Substituted
1	C_2H_5	O	C_2H_5	125—127° (1)	—	84.5
2	C_2H_5	O	C_6H_5	190—192 (1)	—	61.8
3	C_2H_5	O	$NO_2C_6H_4$	201—203 (1)	—	81.3
4	C_2H_5	O	$C_6H_5N_3$	177—178 (0.6)	—	85.7
5	C_2H_5	S	CH_3	135 (0.75)	—	58.2
						4- Substituted
6	CH_3	O	C_6H_5	170—171 (3)	120°	88.6
7	CH_3	S	$NO_2C_6H_4$	—	127—128	86
8	CH_3	S	ClC_6H_4	—	127—131	89.6
9	CH_3	S	CH_3	107—110 (0.5)	—	90
10	CH_3	S	$(C_6H_5)_2CH$	—	57—57.5	82.5
11	C_2H_5	O	CH_3	97 (0.5)	—	82
12	C_2H_5	O	C_6H_5	155—161 (0.5)	—	98
13	C_2H_5	O	$(C_6H_5)_2CH$	203—205 (0.7)	—	66
14	C_2H_5	S	CH_3	—	68	79.5
15	C_2H_5	S	C_6H_5	—	124—125	86
16	C_2H_5	S	$C_6H_5OCH_2$	—	95—97	67
17	C_2H_5	S	$(C_6H_5)_2CH$	—	103—107	89.3
18	C_4H_9	S	C_6H_5	—	115—118	75
19	C_4H_9	S	CH_3	—	102—103	57

in vacuo, and the substance distilled. Yield, 22.6 g (80.2%). A colorless, mobile liquid, readily soluble in water and organic solvents. B.p. 125-126° (3 mm).

Found %: C 65.76; H 9.80; N 15.01. $C_{10}H_{18}ON_2$. Calculated %: C 65.93; H 9.88; N 15.38.

1-Methyl(ethyl)-4-(β-cyanoethyloxy)-piperidines were obtained similarly.

a) 1-Methyl-4-(β-cyanoethyloxy)-piperidine. Yield, 80%, b.p. 125-126° (7 mm), $n^{17}D$ 1.4668.

Found %: C 64.31; H 9.48; N 16.74. $C_9H_{16}ON_2$. Calculated %: C 64.25; H 9.53; N 16.70.

b) 1 Ethyl-4-(β-cyanoethyloxy)-piperidine. Yield, 80%, b.p. 122° (4 mm).

Found %: C 65.48; H 10.01; N 15.30. $C_{10}H_{18}ON_2$. Calculated %: C 65.93; H 9.87; N 15.40.

1-Ethyl-3-(β-carbethoxyethyloxy)-piperidine. a) 22.6 g of 1-ethyl-3-(β-cyanoethyloxy)-piperidine was dissolved in 110 ml of absolute alcohol, and a stream of dry hydrogen chloride bubbled into the reaction mixture for 4 hr, the alcohol meanwhile being stirred and boiled. The ammonium chloride formed was filtered off, the alcoholic solution evaporated in vacuo, the residue treated with a 50% potash solution, and extracted

TABLE 2 (Continued)

Empirical formula	% C		% H		% N		% Cl	
	found	calc.	found	calc.	found	calc.	found	calc.
piperidines								
$C_{13}H_{25}O_3N$	63.92	64.20	10.52	10.30	5.91	5.77	—	—
$C_{17}H_{25}O_3N$	—	—	—	—	5.18	4.81	—	—
$C_{17}H_{24}O_5N_2$	—	—	—	—	8.23	8.34	—	—
$C_{16}H_{24}O_3N_2$	66.04	65.75	8.33	8.22	9.51	9.50	—	—
$C_{12}H_{23}O_2NS$	58.71	58.75	9.62	9.38	5.65	5.72	—	—
piperidines								
$C_{16}H_{23}O_3N \cdot HCl$	60.97	61.35	7.54	7.65	4.72	4.46	11.26	11.35
$C_{16}H_{22}O_4N_2S \cdot HCl$	—	—	—	—	7.34	7.48	9.57	9.49
$C_{16}H_{22}O_2NSCl \cdot HCl$	—	—	—	—	3.88	3.85	19.54 •	19.15 •
$C_{11}H_{21}O_2NS$	—	—	—	—	5.92	6.07	14.06 •	13.87 •
$C_{23}H_{29}O_2NS$	—	—	—	—	3.89	3.65	8.37 •	8.4 •
$C_{12}H_{25}O_3N$	62.52	62.88	10.27	10.04	6.22	6.11	—	—
$C_{17}H_{25}O_3N$	—	—	—	—	4.71	4.81	—	—
$C_{24}H_{31}O_3N$	75.3	75.51	7.5	7.87	3.5	3.68	—	—
$C_{12}H_{23}O_2NS \cdot HCl$	—	—	—	—	—	—	12.65	13.01
$C_{17}H_{25}O_2NS \cdot HCl$	—	—	—	—	3.99	4.07	10.40	10.36
$C_{18}H_{27}O_3NS$	—	—	—	—	3.95	4.15	—	—
$C_{24}H_{31}O_2NS \cdot HCl$	—	—	—	—	3.58	3.2	—	—
$C_{19}H_{29}O_2NS \cdot HCl$	—	—	—	—	3.5	3.77	9.85	9.55
$C_{14}H_{27}O_2NS \cdot HCl$	—	—	—	—	4.2	4.56	11.1	11.5

• Analysis carried out on sulfur.

with ether. The ethereal solution was dried with potash, evaporated in vacuo, and the residue distilled. 18.9 g (66.6%) of 1-ethyl-3-(β-carbethoxyethyloxy)-piperidine was obtained. The substance consisted of a colorless, mobile liquid, readily soluble in water and organic solvents. B. p. 120-121° (3 mm), $n^{17}D$ 1.4589.

Found %: C 62.96; H 9.76. $C_{12}H_{23}O_3N$. Calculated %: C 62.88; H 10.05.

b) A mixture of 3.2 g of 1-ethyl-3-(β-cyanoethyloxy)-piperidine, 10 ml of absolute alcohol, and 4.7 g of concentrated sulfuric acid were boiled for 18 hr. The cooled solution was poured into 70 ml of water, 20 ml of 50% potash solution then added to the acid solution, the precipitated potassium sulfate filtered off, and the alkaline filtrate extracted with ether. After removal of ether, the substance was distilled. 3.1 g (76.8%) of 1-ethyl-3-(β-carbethoxyethyloxy)-piperidine was obtained. B.p. 120-121° (3 mm).

The corresponding 1-alkyl-4-hydroxypiperidine derivatives were obtained by method a.

1-Methyl-4-(β-carbethoxyethyloxy)-piperidine. Yield, 48%. B.p. 102° (2 mm), $n^{18}D$ 1.4558.

Found %: C 60.99; H 9.96; N 6.45. $C_{11}H_{21}O_3N$. Calculated %: C 60.48; H 9.78; N 6.51.

1-Ethyl-4-(β-carbethoxyethyloxy)-piperidine. Yield, 66%. B.p. 113° (4 mm).

Found %: C 62.52; H 10.27; N 6.25. $C_{12}H_{23}O_3N$. Calculated %: C 62.88; H 10.05; N 6.12.

1-Ethyl-3-(γ-hydroxypropyloxy)-piperidine. To a suspension of 0.77 g of lithium alumohydride in 30 ml of absolute ether was added with stirring a solution of 3.1 g of 1-ethyl-3-(β-carbethoxyethyloxy)-piperidine in 30 ml of ether. The mixture was boiled for 3 hr, then cooled and treated with 1.5 ml of water. Lithium and aluminum hydroxides were separated, washed with ether, the ethereal solution dried with potash, evaporated in vacuo, and the residue distilled. 2.2 g (86.8%) of 1-ethyl-3-(γ-hydroxypropyloxy)-piperidine was obtained as a colorless, viscous liquid, readily soluble in water and organic solvents. B.p. 116-118° (3 mm), $n^{17}D$ 1.4749.

Found %: C 64.03; H 11.26; N 7.60. $C_{10}H_{21}O_2N$. Calculated %: C 64.17; H 11.23; N 7.48.

Similar 1-alkyl-4-hydroxypiperidine derivatives were obtained by this method.

1-Methyl-4-(γ-hydroxypropyloxy)-piperidine. Yield, 76.3%. B.p. 114-116° (4 mm), $n^{17}D$ 1.4741.

Found %: C 62.36; H 10.80; N 8.11. $C_9H_{19}O_2N$. Calculated %: C 62.49; H 10.99; N 8.09.

1-Ethyl-4-(γ-hydroxypropyloxy)-piperidine. Yield, 88%. B.p. 125° (5 mm), $n^{24}D$ 1.4713.

Found %: N 7.54; 7.42. $C_{10}H_{21}O_2N$. Calculated %: N 7.48.

1-Ethyl-3-(γ-mercaptopropyloxy)-piperidine. A solution of 2.9 g of 1-ethyl 3-(γ-hydroxypropyloxy)-piperidine in 15 ml of absolute alcohol was acidified with an alcoholic solution of hydrogen chloride, and evaporated in vacuo. To the hydrochloride obtained were added 2.2 g of thionyl chloride, 35 ml of absolute toluene, and the reaction mixture then boiled for 4 hr. The toluene was then distilled off in vacuo, the residue dissolved in 8 ml of water, and, after addition of 15 ml 50% potash solution, extracted with ether. The ethereal solution was dried with sodium sulfate and evaporated in vacuo. 3 g of 1-ethyl-3-(γ-chloropropyloxy)-piperidine was obtained. To convert the chlorine in the latter into a mercapto-group, to the chloride solution in 14.5 ml of 1 N hydrochloric acid was added 1.1 g of thiourea, and the mixture boiled for 6 hr. 1.16 g of caustic soda was then added to the reaction product, the alkaline solution heated on a water bath for 0.5 hr, cooled and extracted with ether. The ethereal solution was dried with sodium sulfate, evaporated in vacuo, and the residue distilled. 2.25 g (71.4%) of 1-ethyl-3-(γ-mercaptopropyloxy)-piperidine was obtained as a colorless, mobile liquid, readily soluble in water and organic solvents. B.p. 132-133° (8 mm).

Found %: C 59.15; H 10.36; N 7.18. $C_{10}H_{21}ONS$. Calculated %: C 59.11; H 10.34; N 6.90.

1-Methyl-4-(γ-mercaptopropyloxy)-piperidine. The hydrochloride of 1-methyl-4-(γ-hydroxypropyloxy)-piperidine (obtained from 10 g of the base), 100 ml of thionyl chloride, and 50 ml of absolute chloroform were boiled for 6 hr. The reaction product was evaporated in vacuo, 4.4 g of thiourea and 56 ml of water added to the residue, and the solution boiled for 5 hr. Further treatment of the reaction product was carried out as described in the preceding experiment. 7.82 g (71%) of 1-methyl-4-(γ-mercaptopropyloxy)-piperidine was obtained. B.p. 100° (0.7 mm).

Found %: C 57.06; H 9.84; S 16.72. $C_9H_{19}ONS$. Calculated %: C 57.11. H 10.05; N 7.45; S 16.94.

1-Ethyl-4-(γ-mercaptopropyloxy)-piperidine was obtained similarly. Yield, 57.2%. B.p. 110° (1 mm).

Found %: C 59.23; H 9.87; N 6.88; S 15.79. $C_{10}H_{21}ONS$. Calculated %: C 59.11; H 10.34; N 6.90.

Di-[γ-(1-ethylpiperidyl-3-oxy)-propyl]-sulfide. The hydrochloride of 1-ethyl-3-(γ-hydroxypropyloxy)-piperidine (obtained from 5.7 g of the base), 40 ml of thionyl chloride, and 80 ml of absolute benzene were heated for 3 hr at 60-65°. The reaction mixture was evaporated in vacuo, the residue made alkaline with a 50% potash solution, and extracted with ether. The ethereal solution was dried with sodium sulfate and the ether distilled off. To the residue, 1-ethyl-3-(γ-chloropropyloxy)-piperidine, was added 2.16 g of thiourea, 16 ml of water, 14 ml of alcohol, and the mixture boiled for 6 hr. After treatment similar to that described in the preceding experiments, the product was distilled in vacuo. 2.5 g (43.2%) of di-[γ-(1-ethylpiperidyl-3-oxy)-propyl]-sulfide was obtained as a yellowish, viscous liquid. B.p. 202-207° (0.5 mm).

Found %: C 63.83; H 10.56; N 7.70; S 8.21. $C_{20}H_{40}O_2N_2S$. Calculated %: C 64.50; H 10.77; N 7.53; S 8.57.

1-Methyl-4-(γ-acetyloxypropyloxy)-piperidine. 2 g of acetyl chloride was added with cooling to a solution of 2.1 g of 1-methyl-4-(γ-hydroxypropyloxy)-piperidine in 20 ml of absolute benzene, and the mixture boiled for 6 hr. The cooled reaction product was treated with 50% potash solution, and the oil separating out extracted

with ether. After drying the ethereal solution with potash and distilling off the solvent in vacuo, the residue was distilled. 2.45 g (94%) of 1-methyl-4-(γ-acetyloxypropyloxy)-piperidine was obtained as a yellow-colored, viscous liquid, soluble in organic solvents, insoluble in water. B.p. 111° (3 mm).

The iodomethylate consisted of colorless crystals, soluble in water, alcohol, and acetone. M.p. 77-79° (from an acetone-ether mixture).

Found %: N 3.94; I 35.81. $C_{12}H_{24}O_3NI$. Calculated %: N 3.92; I 35.63.

1-Methyl-4-(γ-benzoylthiopropyloxy)-piperidine. To a solution of 2 g of 1-methyl-4-(γ-mercaptopropyloxy)-piperidine in 20 ml of absolute ether was added 1.7 g of benzoyl chloride. The reaction mixture was held at room temperature for 48 hr. It was then diluted with 30 ml of ether and the precipitated crystals filtered off. 3.15 g (91%) of the hydrochloride of 1-methyl-4-(γ-benzoylthiopropyloxy)-piperidine was obtained as colorless crystals, soluble in water, alcohol, insoluble in ether. M.p. 129-130° (from acetone).

Found %: N 9.45; S 10.65. $C_{16}H_{23}O_2NS \cdot HCl$. Calculated %: N 9.71; S 10.77.

In Table 2 are shown the physical constants, yield, and results of analyses of esters obtained by one of the two methods described.

4-(β-Cyanoethyloxy)-piperidine. 1.6 g of 4-hydroxypiperidine, 3.25 ml of acrylonitrile, 0.26 g of 30% caustic potash solution in methyl alcohol, and 10 ml of absolute dioxane were reacted in the same manner as that described above in the reaction of 1-alkyl-4-hydroxypiperidines with acrylonitrile. 1.8 g (74.5%) of 4-(β-cyanoethyloxy)-piperidine was obtained as a colorless, highly mobile oil. B.p. 135° (2 mm), $n^{14}D$ 1.4630.

Found %: C 62.01; H 8.88; N 17.73. $C_8H_{14}ON_2$. Calculated %: C 62.41; H 9.09; N 18.15.

4-(β-Carbethoxyethyloxy)-piperidine. A solution of 5 g of 4-(β-cyanoethyloxy)-piperidine in 30 ml of absolute alcohol was saturated at boiling point with dry hydrogen chloride. The ammonium chloride formed was filtered off, the alcoholic solution evaporated in vacuo, the residue made alkaline with 50% potash solution, and extracted with ether. 3.4 g (65.5%) of 4-(β-carbethoxyethyloxy)-piperidine was obtained. B.p. 122° (4 mm).

Found %: C 59.30; H 9.05; N 6.79. $C_{10}H_{19}O_3N$. Calculated %: C 59.70; H 9.45; N 6.96.

1-Butyl-4-(γ-hydroxypropyloxy)-piperidine. To a solution of 1.5 g of 4-(β-carbethoxyethyloxy)-piperidine in 20 ml of piperidine was added 4 g of butyryl chloride and the mixture heated at 65° for 4 hr. Excess butyryl chloride and pyridine were then distilled off in vacuo, the residue dissolved in 10 ml of water, made alkaline with 50% potash solution, and extracted with benzene. The benzene solution was dried with potash, filtered, and added with shaking to a suspension of 0.7 g of lithium alumohydride in 10 ml of absolute ether. The reaction mixture was boiled for 20 hr. 1.4 ml of water was then added, the precipitated lithium and aluminum hydroxides filtered off and washed with ether. After evaporating off solvents, 0.9 g (56%) of 1-butyl-4-(γ-hydroxypropyloxy)-piperidine was obtained as a viscous, yellow-colored liquid, soluble in water and organic solvents. B.p. 130-132° (0.5 mm).

Found %: C 66.70; H 11.20; N 6.08. $C_{12}H_{25}O_2N$. Calculated %: C 67.0; H 11.65; N 6.53.

SUMMARY

The synthesis of esters of 1-ethyl-3-hydroxypiperidine and 1-alkyl-3-(4)-[γ-hydroxy-(thio)-propyloxy]-piperidines is described.

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INVESTIGATION OF THE PHENOXAZINE SERIES

II. PREPARATION OF SEVERAL DERIVATIVES OF SUBSTITUTED PHENOXAZINE-1-CARBOXYLIC ACID

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1893-1897,
June, 1960
Original article submitted June 9, 1959

In the last few years there have been numerous works on the determination of the constitution of a series of actinomycins which are antibiotics with an exceedingly high antibacterial activity [1]; these investigations have shown that the chromophore groups of the majority of them are derivatives of phenoxazine [2]. It is known also that amino-derivatives of phenoxazine possess high antitubercular activity [3].

It was thus of interest to obtain for experiments on antibacterial activity the simplest analogs of actinomycin, viz., derivatives of substituted phenoxazine-1-carboxylic acid, in particular, derivatives of 3-amino-1-phenoxazinoylglycine.

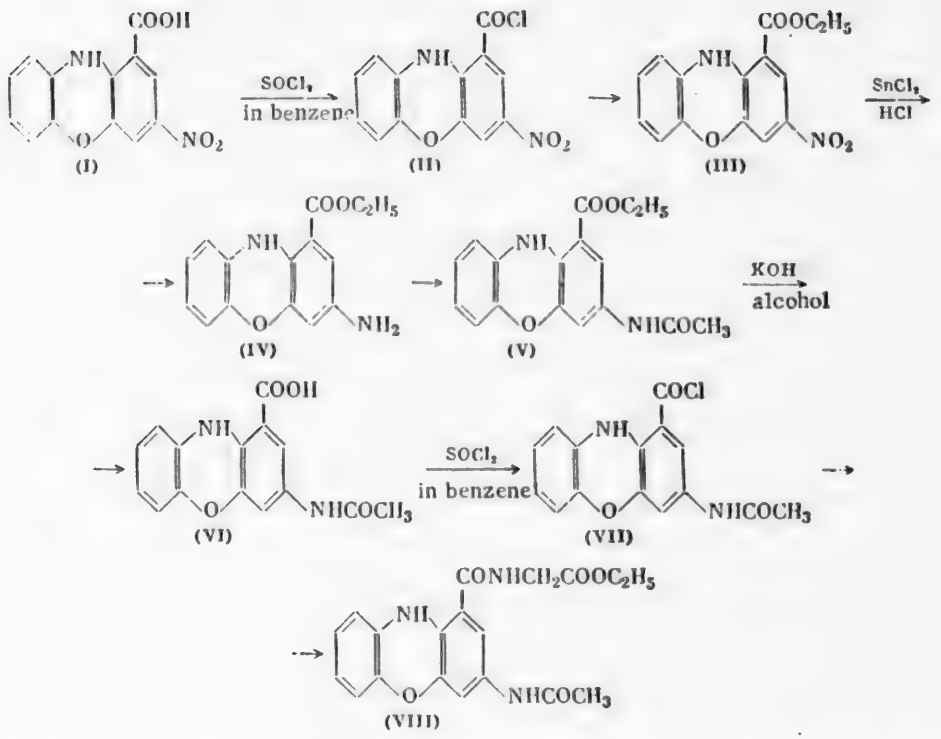
Synthesis was initiated by employing 3-nitrophenoxazine-1-carboxylic acid [3] (I), which, by the action of 3 moles of thionyl chloride in benzene, was converted into its acid chloride (II). From the latter was obtained the ethyl ester (III), which was then reduced with stannous chloride to the ethyl ester of 3-aminophenoxazine-1-carboxylic acid (IV). This compound was converted to the acetylamino-derivative (V), which was hydrolyzed to 3-acetylamino-phenoxazine-1-carboxylic acid (VI) using the calculated quantity of alkali in alcoholic solution.

This series of syntheses was carried out in stages by means of the esters (III, IV, V), because these are more readily isolated in the pure form than the corresponding acids. The acid chloride (VII) of the acid was obtained by reacting with 1 mole of thionyl chloride in benzene solution. The ethyl ester of 3-aceto-amino-1-phenoxazinoylglycine (VIII) was synthesized by condensation of this acid chloride with excess of the glycocollic ester (scheme 1).

During investigation, it was observed that the hydrogens of the phenoxazine ring in positions 1, 3, 6, and 8 possess considerable mobility. 3-Nitrophenoxazine-1-carboxylic acid (I), on boiling with excess thionyl chloride, not only has its hydroxy group converted to chlorine, but also permits the entry of halogen into the 6-position of the ring (IX). Thionyl chloride also substitutes hydrogens in the heterocyclic nucleus on reaction with unsubstituted phenoxazine. This reaction proceeds very vigorously at room temperature. In this case, evolution of sulfur dioxide and sulfur is observed, and after boiling for several minutes tetrachlorophenoxazine is formed. By analogy with the nitration reaction of phenoxazine [4], it may be assumed that substitution by chlorine proceeds in the 1-, 3-, 6-, and 8-positions.

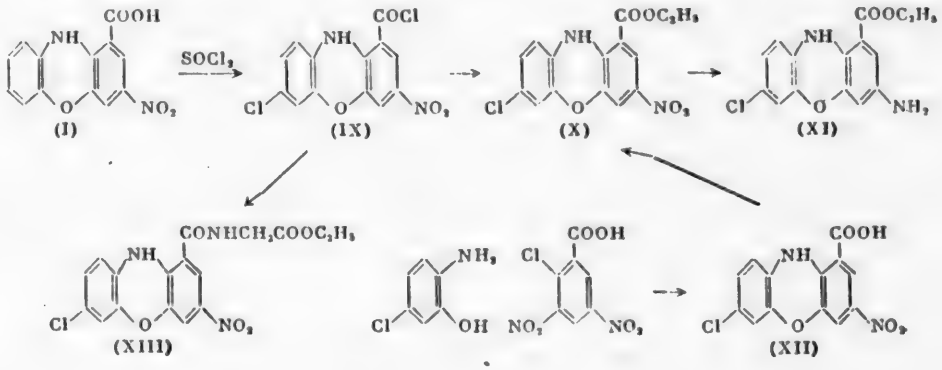
The structure of the ester (X), obtained by chlorination of the acid chloride (IX) as a 6-chloro-substituted compound, was proved in an entirely different manner: from m-chloro-o-aminophenol [5] by condensation with 2-chloro-3, 5-dinitrosalicylic acid, 4'-chloro-2'-hydroxy-2-carboxy-4, 6-dinitrodiphenylamine was obtained, which on reacting with alkali gave 6-chloro-3-nitrophenoxazine-1-carboxylic acid (XII). The ethyl ester obtained from it did not give depression of melting point when a sample was mixed with (X).

Scheme 1



The ethyl ester of 6-chloro-3-nitrophenoxazine-1-carboxylic acid (X) was reduced to the corresponding amino-ester (XI), and the ethyl ester of 6-chloro-3-nitro-1-phenoxazinoylglycine (XIII) was obtained by condensation of the acid chloride (IX) with the glycocoll ester. It was not possible to reduce the nitro-group in this substance to an amino-group, as in the various reduction methods used, including a catalytic one, only a solid, black, insoluble tar was formed (see scheme 2).

Scheme 2



EXPERIMENTAL

1. Ethyl ester of 3-nitrophenoxazine -1-carboxylic acid (III). A mixture of 20 g of 3-nitrophenoxazine-1-carboxylic acid (I), 300 ml of absolute benzene, and 20 ml of thionyl chloride were boiled for 1.5 hr. The acid chloride of 3-nitrophenoxazine-1-carboxylic acid (II) separated out on cooling as dark-brown needles. 10 g of acid chloride of m.p. 178-181°C, obtained by recrystallization from benzene, was heated with 250 ml of absolute alcohol for 1 hr. The brown residue turned bright-red without dissolving. After recrystallization from alcohol 8 g of the ester (III) of m.p. 205-206° was obtained.

Found %: C 60.33; H 4.08; N 8.69. $C_{15}H_{12}O_5N_2$. Calculated %: C 60.25; H 3.68; N 9.25.

2. Ethyl ester of 3-aminophenoxazine-1-carboxylic acid (IV). This was obtained from (III) by the method indicated in Expt. 9. On recrystallization from alcohol the compound formed dark-yellow needles, darkening on storage (especially when exposed to light), with m.p. 149-150°.

Found %: C 66.69; H 5.32; N 10.37. $C_{15}H_{14}O_3N_2$. Calculated %: C 66.66; H 5.19; N 10.37.

3. Ethyl ester of 3-acetylaminophenoxazine-1-carboxylic acid (V). This was obtained by boiling the ester (IV) with acetic anhydride for 5 min. Dark-yellow needles with m.p. 222° (from acetic acid).

Found %: C 64.93; H 5.10; N 9.33. $C_{17}H_{16}O_4N_2$. Calculated %: C 65.38; H 5.13; N 8.97.

4. 3-Acetylaminophenoxazine-1-carboxylic acid (VI). A mixture of 4.3 g of the ester (V), 0.8 g of caustic potash, and 100 ml of alcohol was boiled for 30 min. After cooling, the solution was neutralized with concentrated hydrochloric acid. 3.6 g of (VI) was obtained, which on recrystallization from a very large quantity of acetic acid gave pale-yellow needles of m.p. 305°.

5. Ethyl ester of 3-acetylamino-1-phenoxazinoylglycine (VIII). A mixture of 10 g of the acid (VI), 4.15 g of thionyl chloride, and 200 ml of absolute benzene was boiled for 2 hr. To the resulting 10 g of acid chloride (VII) in 250 ml of absolute benzene was added 8.5 g of the ethyl ester of glycocoll in 10 ml of benzene. After boiling for 1 hr 14.5 g of (VIII) was obtained. Bright-yellow needles of m.p. 206-209° (from alcohol).

Found %: C 61.54; H 5.28; N 11.60. $C_{19}H_{19}O_5N_3$. Calculated %: C 61.78; H 5.15; N 11.35.

6. Ethyl ester of 6-chloro-3-nitrophenoxazine-1-carboxylic acid. 2.5 g of 3-nitrophenoxazine-1-carboxylic acid (I) was boiled for 2 hr with 25 ml of thionyl chloride. The resulting 2 g of acid chloride of 6-chloro-3-nitrophenoxazine-1-carboxylic acid (IX) was heated with 50 ml of absolute alcohol. The residue of acid chloride was insoluble. Its color gradually changed from brown to bright-yellow, and the acid chloride changed to the ethyl ester (X). Yield 1.9 g. Reddish-orange needles of m.p. 183-184° (from glacial acetic acid).

Found %: N 8.44; Cl 9.75. $C_{15}H_{11}O_5N_2Cl$. Calculated %: N 8.36; Cl 10.61.

7. 1, 3, 6, 8-Tetrachlorophenoxazine. To 1 g of phenoxazine was added 10 ml of thionyl chloride, slight evolution of heat and extreme frothing occurring. After evolution of gas had ceased, the mixture was boiled for 5-10 min. A voluminous white precipitate separated from the dark-green reaction mixture. 1.6 g of tetrachlorophenoxazine was obtained, with m.p. 222-223° (from a large quantity of glacial acetic acid).

Found %: Cl 43.97. $C_{12}H_5ONCl_4$. Calculated %: Cl 44.11.

8. 6-Chloro-3-nitrophenoxazine-1-carboxylic acid (XII). A mixture of 24 g of 2-chloro-3,5-dinitrobenzoic acid, 14 g of m-chloro-o-aminophenol, 14 g of calcined sodium acetate, and 150 ml of absolute alcohol was boiled for 2 hr. The resulting solution was poured into 300 ml of water and neutralized with dilute hydrochloric acid. The black oil separating out crystallized into a red precipitate of 4'-chloro-2'-hydroxy-2-carboxy-4,6-dinitrodiphenylamine, which was washed with water and dissolved in a small quantity of 5% caustic solution. After boiling for 3 min a dense, dark-brown precipitate of the nitrate of 6-chloro-3-nitro-phenoxazine-1-carboxylic acid separated out from solution. After cooling, the precipitate was filtered off, stirred with 400 ml of water, and treated with dilute hydrochloric acid. The recrystallized acid did not melt when heated to 350°. Dark-red crystals; yield, 15 g.

Found %: Cl 11.00. $C_{13}H_7O_5N_2Cl$. Calculated %: Cl 11.55.

From the acid (XII) was obtained the ethyl ester of m.p. 184°, which did not give a depression of melting point when a sample was mixed with the ethyl ester (X) obtained earlier.

9. Ethyl ester of 6-chloro-3-aminophenoxazine-1-carboxylic acid (XI). A solution of 3.8 g of stannous chloride in 15 ml of concentrated hydrochloric acid was added to 1.5 g of the ester (X) in 15 ml of boiling alcohol. The precipitate changed from red to yellow. After addition had been completed, the mixture was heated for a further 5-10 min. The yellow precipitate of stannic complex separating out on cooling was dissolved in methane and the ester (XI) was separated from the solution by using 5% caustic. The ester took the form of dark-yellow needles of m.p. 162-164° (from alcohol). The acetyl derivative of the ester, obtained by boiling with acetic anhydride for 5 min, took the form of bright-yellow needles of m.p. 214-215° (from acetic acid).

Found %: C 58.91; H 4.29; N 8.98; Cl 11.63. $C_{15}H_{13}O_3N_2Cl$. Calculated %: C 59.11; H 4.27; N 9.18; Cl 11.65.

10. Ethyl ester of 6-chloro-3-nitro-1-phenoxazinoylglycine (XIII). 4 g of the ethyl ester of glycocoll in 10 ml of absolute benzene was added to 5.6 g of the acid chloride (IX) in 100 ml of boiling absolute benzene, and heated for 1.5 hr. 9.7 g of (XIII) was obtained as bright-red needles of m.p. 187° (from acetic acid).

Found %: C 52.29; H 3.73; N 10.79; Cl 8.22. $C_{17}H_{14}O_6N_3Cl$. Calculated %: C 52.10; H 3.57; N 10.75; Cl 9.08.

SUMMARY

1. Synthesis of 3-acetamino-1-phenoxazinoylglycine and 6-chloro-3-nitro-1-phenoxazinoylglycine was accomplished in a series of stages.

2. It was shown that on reacting phenoxazine with excess thionyl chloride the substitution of the hydrogens of the heterocycle by chlorine proceeds readily, with formation of 1,3.6,8-tetrachlorophenoxazine.

Under the same conditions the hydrogen in the 6-position in 3-nitrophenoxazine-1-carboxylic acid is substituted by chlorine.

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POLYNUCLEAR HETEROCYCLIC COMPOUNDS

III. 1-ACENAPHTHENONE-SPIRO-(2 : 4')-2',3'(CO),6',5'(CO)-DIBENZOYLENDIHYDROPYRIDINE

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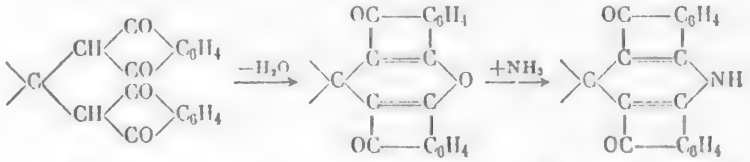
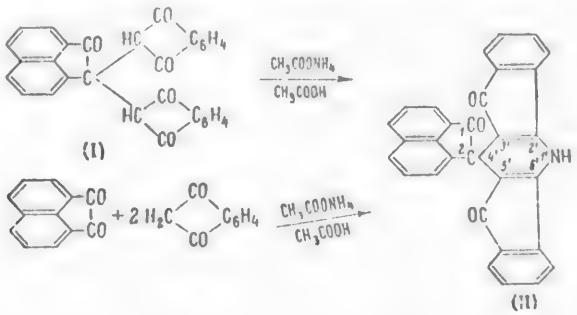
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1898-1904,
June, 1960
Original article submitted June 10, 1959

In a series of studies [1-6] by one of us with L. S. Geita, it was shown that geminal diindandionyl derivatives, reacting in the enol form, under the influence of water-removing substances split out a molecule of water and are converted into the corresponding pyrane. The latter, under the influence of ammonia or amines replaces the oxygen bridge by nitrogen and gives the corresponding dihydropyridine.

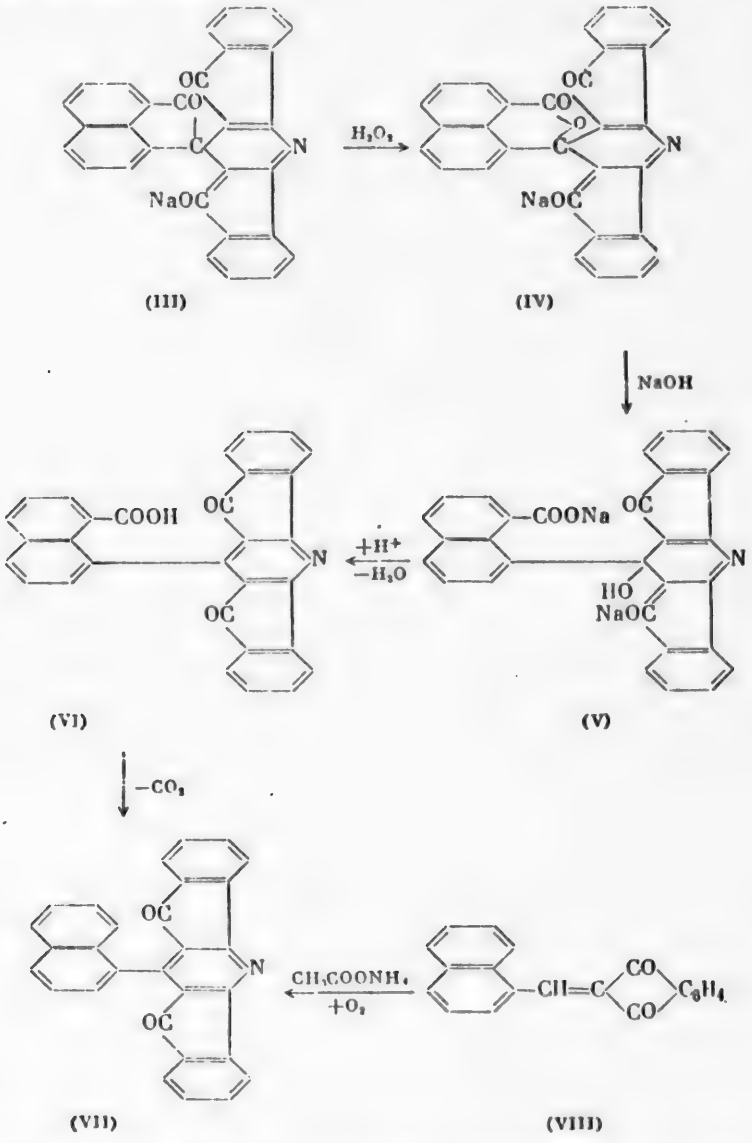


The replacement of the oxygen in the pyrane by nitrogen also often occurs even under the action of an alcohol solution of ammonia or amine on the pyrane, but sometimes only by heating in a sealed tube with liquid ammonia; this, however, is not a suitable method for obtaining these dihydropyridines. Recently, in the case of trisindandione we found [7] that, passing over the stage of the pyrane, we could obtain the corresponding dihydropyridine directly by heating geminal diindandionyl derivatives with ammonium acetate in glacial acetic acid. In order to discover whether this reaction was more general, we treated 2,2-diindandionylacetonaphthen-1-one (I) [3] in an analogous way. We showed that under the action of ammonium acetate it gives a dihydropyridine, namely 1 acenaphthenone-spiro-(2 : 4')-2',3'(CO),6',5'(CO)-dibenzoylendihydropyridine (II), whose properties agree with those of the product obtained from the corresponding pyrane [4]. The dihydropyridine (II) is obtained still more simply by heating a mixture of indandione, acenaphthoquinone and ammonium acetate in glacial acetic acid. This method recalls the synthesis of dihydropyridine according to Hantzsch [8] using as the carbonyl derivative in our case the acenaphthenquinone.



In the latter case practically no side products are obtained and we obtain only the pure acenaphthenone-spiro-dihydropyridine (II), although it is known [9-11] that acenaphthenone easily reacts with ammonia or ammonium acetate. To remove some of the starting substance, the raw product (II) was boiled thoroughly with glacial acetic acid or recrystallized from acetic acid, chloroform, or dioxane. From pyridine the substance (II) crystallizes with a half molecule of pyridine which is not removed even by heating the compound, but which is removed by boiling with methanol. It was observed previously that some dihydropyridines form a labile bond with ammonia [4].

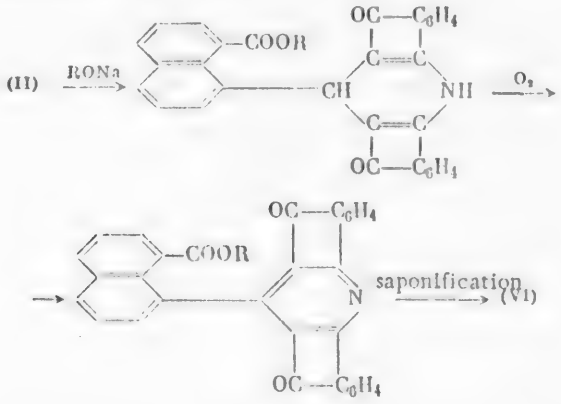
The dihydropyridine (II) is soluble in water or alcoholic alkali, concentrated ammonia and piperidine, with a green color which is evidently connected with the formation of the enolate (III); on acidification the unchanged original product precipitates.



Under the action of hydrogen peroxide on an alkaline solution of (II), that is on (III), even at ordinary temperature there is oxidation to the carboxylic acid. Since splitting at the benzoylene group in other dibenzoyl-enpyridines does not occur, it must be thought that there is splitting of the acenaphthene ring with formation of the corresponding lactone (IV) [12, 13]. The resulting lactone in an alkaline medium is split with formation of the sodium salt of 8-[2',3'(CO),6',5'(CO)-dibenzoylen-4'-hydroxy-4'-dihydropyridyl]-1-naphthoic acid (V); the

latter then splits out a molecule of water and gives the sodium salt of 8-[2',3'(CO),6',5'(CO)-dibenzoylen-4'-pyridyl]-naphthoic acid. Acidification of the solution precipitates the acid (VI) itself in the form of a yellow solid.

The acid (VI) is soluble in alkalis and also in sodium bicarbonate, with a yellow color. We have prepared in pure form the sodium, potassium, ammonium, piperidine, and triethanolamine salts of this acid. By the action of thionyl chloride on acid (VI) we have obtained its acid chloride, and from this the methyl and ethyl esters. These esters can also be obtained directly from the dihydropyridine (II) when it is split with sodium methylate or ethylate in the corresponding alcohol. In this case we must expect formation of the dihydro derivative, but we obtain esters of the same acid (VI); evidently the dihydro derivative first formed at once is oxidized in the alkaline medium by the oxygen of the air into the pyridine derivative. The resulting esters are saponified by 80% sulfuric acid with formation of acid (VI). When acid (VI) is heated in quinoline with freshly reduced copper powder there is decarboxylation with formation of 4-(α-naphthyl)-2,3(CO),6,5(CO)-dibenzoylenpyridine (VII) which is not soluble even in bicarbonate and alkali.



In order to show the correctness of our assumed structure for compound (VII) we tried to synthesize it by the method worked out earlier. By condensation of α-naphthaldehyde with indandione we prepared the already known α-naphthalindandione (VIII) [14, 15]. However, the latter, in distinction from benzalindandione did not condense further with one molecule of indandione. Using another method for obtaining pyridines [16, 17], namely, direct heating of naphthalindandione with ammonium acetate in glacial acetic acid, we were able to obtain naphthyldibenzoylenpyridine (VII), a product entirely analogous in properties to that obtained by decarboxylation of acid (VI). Thus, the correctness of the structure of the acenaphthenone-spiro-dibenzoylendihydropyridine (II), can be considered to be established.

EXPERIMENTAL

1-Acenaphthenone-spiro-(2 : 4')-dibenzoylen-2',3'(CO),6'5'(CO)-dihydropyridine (II). a) (From 2,2-diindandionyl-1-acenaphthenone). One g of 2,2-diindandionyl-1-acenaphthenone was dissolved with boiling in 90 ml of glacial acetic acid; to the solution was added 10 g of ammonium acetate, it was boiled three hours, several ml of water were added, and it stood for several hours. The precipitate of 1-acenaphthenone-spiro-(2 :4')-dibenzoylen-2',3'(CO),6',5'(CO)-dihydropyridine was separated and boiled first with 100 ml of 2% ammonia and then with 200 ml of water. Red crystals with m.p. 270-275°. (In paper [4] 374-376° was evidently erroneously reported instead of 274-276°.)

Found %: N 3.42. $C_{30}H_{15}O_3N$. Calculated %: N 3.20.

b) (From indandione and acenaphthenquinone.) Three g of acenaphthenquinone was dissolved with heating in 80 ml of glacial acetic acid and the solution was treated with a solution of 4.8 g of indandione in 30 ml of glacial acetic acid and 1 ml of concentrated hydrochloric acid. The mixture was boiled for 3-5 min, 13 g of ammonium acetate was added together with several pieces of porous plate, and it was boiled for one hour. On the next day the precipitate was separated, boiled with 100 ml of 80% acetic acid, filtered hot, and washed with methyl alcohol. Yield 5.75-6.35 g (79.5-88.3%). Red crystals with m.p. 264°.

Found %: N 3.06. $C_{30}H_{15}O_3N$. Calculated %: N 3.20.

1-Acenaphthenone-spiro-(2 : 4')-dibenzoylen-2',3'(CO),6',5'(CO)-dihydropyridine in sodium hydroxide and concentrated ammonia dissolved with an emerald green color, dissolved still more easily in alcoholic alkali or alcoholate, and did not dissolve in 2% ammonia even on boiling. It crystallized from dioxane, chloroform and glacial acetic acid. Slightly soluble in isobutyl alcohol and acetone, almost insoluble in methanol, ethanol, and carbon tetrachloride. In piperidine it dissolved with a green color, and in pyridine, with a red color; from this a substance crystallized which contained 0.5 molecule of pyridine, m.p. 270°.

Found %: N 4.56 (air dried); 4.37 (dried at 80°). $2C_{30}H_{15}O_3N \cdot C_5H_5N$. Calculated %: N 4.41.

When it was boiled with methanol, the pyridine was removed.

Found %: N 3.19. $C_{30}H_{15}O_3N$. Calculated %: N 3.20.

8-[2',3'(CO),6',5'(CO)-Dibenzoylen-4'-pyridyl]-1-naphthoic acid (VI). Eight g of 1-acenaphthene-spiro-(2 : 4')-dibenzoylen-2',3'(CO),6',5'(CO)-dihydropyridine was suspended in 150 ml of methanol and treated with a solution of 2 g of sodium hydroxide in 150 ml of methanol and 8 ml of 30% hydrogen peroxide. On the next day the green solution had become yellow and there was a yellow precipitate of the crystalline Na salt. Yield 4.80 g. The filtrate was diluted with water and acidified with hydrochloric acid. We obtained 3.55 g of yellow crystalline acid (VI). The substance dissolved in sodium bicarbonate, in alcoholic alkali, concentrated ammonia, chloroform, glacial acetic acid, and dioxane. One g of the Na salt was recrystallized from 55 ml of glacial acetic acid and gave 0.57 g of 8-[2',3'(CO)-6',5'(CO)-dibenzoylen-4'-pyridyl]-1-naphthoic acid, m.p. 335° (decomposition); after crystallization from dioxane, m.p. 334°.

Fouhd %: N 3.01, 3.09. $C_{30}H_{15}O_4N$. Calculated %: N 3.09.

Ammonium salt. a) Acid (VI) was boiled with concentrated ammonia and the hot solution was filtered. After cooling, fine orange crystals of the ammonium salt precipitated. Slightly soluble in water. M.p. 325° (decomp.).

b) Acid (VI) was suspended in dioxane, concentrated ammonia was added, it was boiled, and the hot solution was filtered. Fine yellow crystals precipitated. M.p. 328° (decomp.).

Found %: N 5.59. $C_{30}H_{18}O_4N_2$. Calculated %: N 5.95.

Sodium salt. This was obtained by splitting the acenaphthenone spiro-dibenzoylendihydropyridine (II) with alcoholic alkali and hydrogen peroxide. It is sufficiently soluble in water and on heating forms about a 8.5% solution which crystallizes with cooling. The crystals contain two molecules of water of crystallization. They melt with decomposition above 360°.

Found %: H_2O 7.13. $C_{30}H_{14}O_4NNa \cdot 2H_2O$. Calculated %: H_2O 7.14.
Found %: N 2.85, Na 4.73. $C_{30}H_{14}O_4NNa$. Calculated %: N 2.95; Na 4.84.

Potassium salt. Obtained in a manner analogous to the sodium salt. It dissolves slightly in water; better in a mixture of ethanol and water (1 : 1).

Found %: N 2.68; K 7.54. $C_{30}H_{14}O_4NK$. Calculated %: N 2.85; K 7.96.

Piperidine salt. Acid (VI) was boiled with 50% alcohol, piperidine was added and it was filtered. Yellow bipyramids. To remove any possible unreacted acid, we boiled the salt crystals with dioxane. M.p. 295° (decomp). Slightly soluble in water and alcohol, not soluble in dioxane.

Found %: N 5.27. $C_{35}H_{26}O_4N_2$. Calculated %: N 5.20.

Triethanolamine salt. Acid (VI) was boiled in 10% alcoholic solution of triethanolamine and the resulting precipitate was washed with alcohol and boiled with dioxane. M.p. 243-244° (decomp). Little soluble in water methanol, and ethanol.

Found %: N 4.57. $C_{36}H_{30}O_7N_2$. Calculated %: N 4.63.

Acid chloride of (VI). On a water bath we boiled 1.8 g of acid and 20 ml of thionyl chloride for 1.5 hr; the excess thionyl chloride was removed and the residue was crystallized from dry toluene. We obtained 1.2 g of yellow crystals. M.p. 285° (decomp). The crystalline substance did not react with concentrated ammonia in the cold, but with heating it dissolved somewhat with a red-violet color; with dilute alkali it reacted easily.

Found %: N 3.05; Cl 7.61, 7.79. $C_{30}H_{14}O_3NCl$. Calculated %: N 2.97; Cl 7.52.

Methyl ester of acid (VI). The acid chloride of (VI) (0.38 g), 20 ml of anhydrous chloroform, and 2 ml of anhydrous methanol were boiled for two hours, the chloroform was removed, and the yellow residue was crystallized from glacial acetic acid. M.p. 288-292°.

Found %: N 2.90, 3.05. $C_{31}H_{17}O_4N$. Calculated %: N 3.00.

Ethyl ester of acid (VI). By boiling for four hours a mixture of 0.25 g of acid chloride and 4 ml of anhydrous ethanol in 20 ml of chloroform, we obtained the above ester. Yellow crystals, m.p. 290°. Easily soluble in dioxane and toluene, less so in glacial acetic acid.

Found %: N 3.02, 3.09. $C_{32}H_{19}O_4N$. Calculated %: N 2.91.

Splitting of acenaphthenone-spiro-dibenzoylendihydropyridine (II) by alcoholates. a) (By sodium methylate). Two g of substance (II) and 65 ml of 3% sodium methylate in methanol were boiled for three hours on the water bath. We obtained a green solution with a yellow crystalline precipitate. This was separated and crystallized from glacial acetic acid. M.p. 282-286°. A mixture with the methyl ester of (VI) obtained from the acid chloride melted without depression.

Found %: N 3.24, 2.91. $C_{31}H_{17}O_4N$. Calculated %: N 3.00.

b) (By sodium ethylate). We carried out the reaction as above. The resulting ethyl ester was twice recrystallized from glacial acetic acid. M.p. 290°. The product gave no depression of melting point with the ethyl ester obtained from the acid chloride of (VI).

Found %: N 2.96. $C_{32}H_{19}O_4N$. Calculated %: N 2.91.

Saponification of the ethyl ester of acid (VI). The ethyl ester (0.2 g) and 20 ml of 80% sulfuric acid were heated to 130°; the ester dissolved and then platelets precipitated. After cooling, the mixture was diluted with ten times the amount of water, the precipitate was separated, dissolved in concentrated ammonia, and the filtrate was acidified. The precipitate was crystallized from dioxane. M.p. 335-337°. A mixture with acid (VI) melted without depression of the melting point.

Found %: N 3.04. $C_{30}H_{15}O_4N$. Calculated %: N 3.09.

4-(α-naphthyl)-2,3(CO),6,5(CO)-dibenzoylenpyridine (VII). a) [By decarboxylation of acid (VI)]. Acid (VI) (0.8 g), 0.8 g of freshly reduced copper powder, and 20 ml of quinoline were boiled for four hours, cooled, and diluted with five times the amount of ether. On the next day the liquid was poured off from the yellow precipitate which had formed, the precipitate was separated and the 0.62 g of substance obtained was twice recrystallized from dioxane. The yellow crystals of 4-(α-naphthyl)-2,3(CO),6,5(CO)-dibenzoylenpyridine melted at 395°. They did not dissolve in concentrated ammonia or alkali.

b) (From α-naphthalindandione.) α-Naphthalindandione (VIII) (1.5 g) and 10 g of ammonium acetate in glacial acetic acid were boiled for one hour. The yellow precipitate (0.72 g) was recrystallized from 200 ml of dioxane, then from glacial acetic acid. M.p. 395°.

Found %: N 3.41, 3.59. $C_{29}H_{15}O_2N$. Calculated %: N 3.42.

SUMMARY

By the action of ammonium acetate in glacial acetic acid on 2,2-diindandionyl-1-acenaphthenone we have obtained 1-acenaphthenone-spiro-(2 : 4')-2',3'(CO),6',5'(CO)-dibenzoylendihydropyridine. The latter compound has also been obtained directly by heating a mixture of acenaphthenquinone, indandione, and ammonium acetate in glacial acetic acid.

Under the action of hydrogen peroxide an alkaline solution of 1-acenaphthenone-spiro-(2 : 4')-2',3'(CO),6',5'(CO)-dibenzoylendihydropyridine is transformed by splitting of the five membered acenaphthene ring with formation of 8-[2',3'(CO),6',5'(CO)-dibenzoylen-4'-pyridyl]-1-naphthoic acid. Esters of the same acid are obtained by splitting 1-acenaphthenone-spiro-(2 : 4')-2',3'(CO),6',5'(CO)-dibenzoylendihydropyridine by alcoholates. Decarboxylation of the acid in quinoline in the presence of copper powder gives 4-(α-naphthyl)-2,3(CO),6,5(CO)-dibenzoylenpyridine, prepared in another synthesis from α-naphthalindandione (obtained from α-naphthaldehyde and indandione) and ammonium acetate in glacial acetic acid.

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THE SULFONATION OF β-DIKETONES

X. SULFONATION OF DIMEDON

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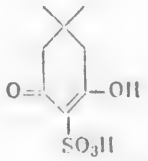
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1904-1911,
June, 1960
Original article submitted June 20, 1959

Dimedon is easily sulfonated by dioxane sulfotrioxide [1] and also by 100% sulfuric acid in the presence of acetic anhydride in a solution of 1,2-dichloroethane [2, 3] and other solvents [4].

In the present work we have studied the effect of concentration of sulfuric acid on the reaction of sulfonation of dimedon in 1,2-dichloroethane solution in the presence of different amounts of acetic anhydride.

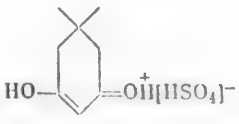
In the case of sulfonation by 99.5% sulfuric acid the best yield of dimedon sulfonic acid (I) is obtained at a ratio of acetic anhydride to sulfuric acid of 1 : 1, as the data in Table 1 show. Sulfuric acid alone does not sulfonate dimedon.



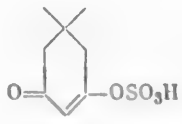
(I)

In the sulfonation of dimedon by 86% sulfuric acid, whose composition is close to the formula $H_2SO_4 \cdot H_2O$, twice as much acetic anhydride must be taken as with 99.5% sulfuric acid in order to obtain a good yield of dimedon sulfonic acid, as the results in Table 2 show.

If there is not enough acetic anhydride for a given concentration of sulfuric acid, the chief product is a substance which can be considered either as dimedon hydrogen sulfate (II), or as the ester of the enol form of dimedon and sulfuric acid (III).

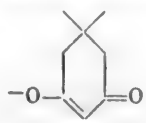


(II)



(III)

In studying solutions of dimedon in concentrated sulfuric acid, Eistert and co-workers [5] suggested the possibility of formation of the hydrogen sulfate (II). They confirmed this by the ultraviolet spectra. In their opinion the bathochromic shift in alkaline and acid media indicated the presence of the enolate ion (IV) and the oxonium cation (V) respectively, which have structural chromophoric systems close to each other.



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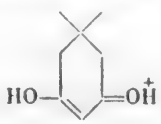


(V)

TABLE 1

Sulfonation of Dimedon by 99,5% Sulfuric Acid

No.	Reacting substances (in moles)			Yield of dimedon-sulfonic acid (in %)
	dimedon	99.5% sulfuric acid	acetic anhydride	
1	(I)	1.3	1.3	95—98
2	(I)	1.3	0.65	42
3	(I)	1.3	0	0

Note: Duration of reaction 30 min, temperature 40-50°.

TABLE 2

Sulfonation of Dimedon by 86% Sulfuric Acid

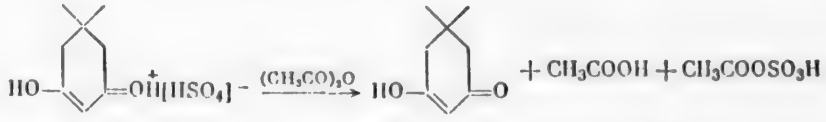
No.	Reacting substances (in moles)			Yield of dimedon-sulfonic acid (in %)
	dimedon	86% sulfuric acid	acetic anhydride	
1	(I)	1.3	1.3	21.5
2	(I)	1.3	2.6	91.5
3	(I)	1.3	3.9	97.6

Note: Duration of reaction 30 min, temperature 40-50°.

In order to make a choice between structures (II) and (III) we studied the resulting products in greater detail, since literature data on them scarcely exists. Our study showed that structure (II) is more probable, that is, dimedon hydrogen sulfate.

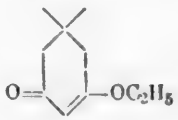
Dimedon hydrogen sulfate (II) is a white, crystalline substance with m.p. 140-141°. In air it quickly absorbs water, and in water it immediately splits into sulfuric acid and dimedon.

In the reaction of acetic anhydride with dimedon hydrogen sulfate at 40° it dissolves, and on cooling, crystals of dimedon sulfonic acid precipitate. The reaction obviously occurs with formation of acetyl sulfuric acid (VI) which reacts with dimedon and forms dimedon sulfonic acid [2].



(VI)

It seems of interest to study the reaction of dimedon hydrogen sulfate with anhydrous alcohol, since in the synthesis of dimedon ethyl ether (VII) p-toluenesulfonic acid is used as a catalyst [6, 7]. It was shown that dimedon hydrogen sulfate, reacting with anhydrous ethanol, easily formed dimedon ethyl ether (VII) in 82% yield.



(VII)

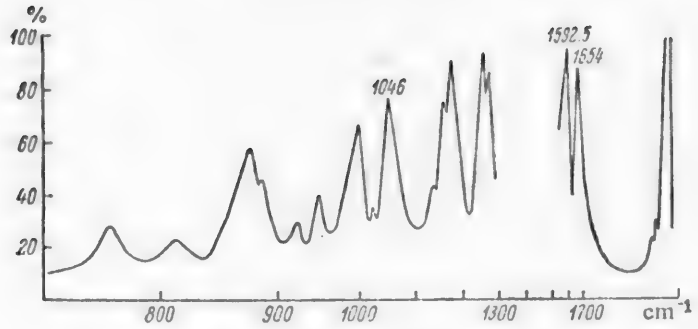
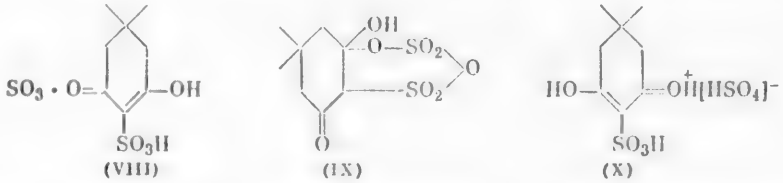


Fig. 1. Infrared spectrum of sodium dimedon sulfonate.

We did not obtain the phenyl ether under analogous conditions, which indicates structure (II) and not (III), since, as is known, such esters of sulfuric acid are good alkylating agents and form phenyl ethers [8]. The product does not form salts and when it is ground with sodium carbonate or acetate it gives dimedon and sodium sulfate, which also indicates structure (II).

Dimedon is also easily sulfonated by sulfuric anhydride in anhydrous chloroform solution. At a mole ratio of dimedon: sulfuric anhydride of 1 : 1 there is a 92% yield of dimedon sulfonic acid. At a mole ratio of 1 : 2, a white, hygroscopic substance is obtained. Water decomposes it to dimedon sulfonic acid and sulfuric acid at once. This compound can be assigned the formula (VIII) [9] or (IX) [10, 11], or even (X). The latter compound could be formed in the presence of water although reaction in this case is carried out in anhydrous chloroform. This question demands further study, however.



The mechanism of the reaction of sulfonation of dimedon in nonpolar solvents depends on the nature of the sulfonating agent. It is most probable that dimedon itself reacts in its enol form, as was already reported earlier [2]. Although the reaction occurs in nonpolar solvents where the keto form of dimedon also exists [12], yet sulfuric acid and acetic anhydride can shift the equilibrium of tautomeric forms of dimedon toward its enol form [5, 13].

In its properties, dimedon sulfonic acid resembles the aromatic hydroxysulfonic acids. It is easily hydrolyzed by concentrated hydrochloric acid like phenol [14] and naphthol sulfonic acids [15]. On the other hand, dimedon sulfonic acid is a β-ketosulfonic acid. By analogy with the β-ketocarboxylic acids it should split off sulfuric anhydride.

It is known that when acetone sulfonic acid is heated with phosphoric or sulfuric acid it evolves sulfurous and not sulfuric anhydride [16]. With careful heating to 102-105° of dimedon sulfonic acid itself or its suspension in anhydrous toluene, it melts. After cooling, dimedon hydrogen sulfate (II) is obtained. Evidently, heating evolves sulfuric anhydride, which perhaps absorbs moisture from the air and forms sulfuric acid and the latter with dimedon gives the dimedon hydrogen sulfate (II).

Dimedon sulfonic acid forms salts which are easily soluble in water [3]. In order to explain the structure of the salts we took the infrared spectra for the sodium and ammonium salts of dimedon sulfonic acid (Figs. 1 and 2). It is clear from the spectra that the frequencies of the ketogroup in the dimedon sulfonic acid salts are lowered (1654 cm^{-1} for the sodium salt and 1637 cm^{-1} for the ammonium salt) as compared to the uncombined carbonyl group, and in the spectra appear frequencies for double carbon-carbon bonds (1592 cm^{-1} for the sodium salt and 1567 cm^{-1} for the ammonium salt). This means that the salts of dimedon sulfonic acid are enols in the crystalline state.

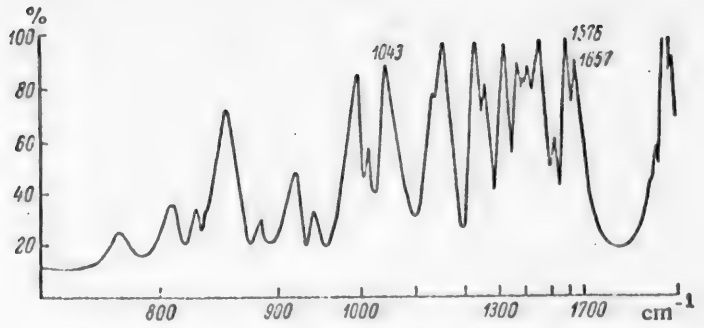


Fig. 2. Infrared spectrum of ammonium dimedon sulfate.

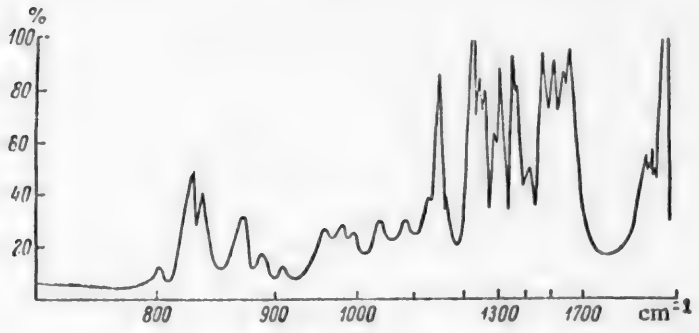


Fig. 3. Infrared spectrum of dimedon.

In the spectra of dimedon sulfonic acid salts (Figs. 1 and 2) there are the characteristic frequencies of symmetrical valence oscillations of the sulfur-oxygen bond (1043 and 1046 cm^{-1}). It is difficult to identify the frequencies of unsymmetrical valence oscillations of the sulfur-oxygen bond (1210-1150 cm^{-1}), since in this region are the frequencies of dimedon itself (1260-1150 cm^{-1}) (Fig. 3).

EXPERIMENTAL

Dimedon sulfonic acid. a) Sulfonation of dimedon by 99.5% sulfuric acid. A mixture of 0.7 ml of 99.5% sulfuric acid, 1.3 ml of acetic anhydride, and 1.4 g of dimedon in 4 ml of 1,2-dichloroethane was heated for 30 min on a water bath at 40°. The dimedon dissolved and the solution took on a brownish color. The mixture was cooled to 0°. After several hours crystals of dimedon sulfonic acid appeared. The crystals were well washed with 1,2-dichloroethane. The sulfonic acid could not be recrystallized. We obtained 1.55 g (70.5%) of dimedon sulfonic acid. M.p. 101-102° (according to the literature 90-91° [3], 119-121° [17]). Since, when forms of the sulfonic acid with m.p. 101-102° and 90-91° were mixed, the mixture melted without lowering of the melting point at 100-101°, the differences in melting point given by different authors are evidently caused by different rates of heating and the resulting conversion of dimedon sulfonic acid into dimedon hydrogen sulfate.

The solution of 1,2-dichloroethane was washed with water after separation of the dimedon sulfonic acid. The water solution was neutralized with sodium carbonate to pH 5 and the dimedon sulfonic acid was salted out with sodium chloride. We obtained 0.75 g of the sodium salt of dimedon sulfonic acid, which corresponded to a total yield of 97.5%.

If in the sulfonation of dimedon we used 0.5 mole acetic anhydride per mole of 99.5% sulfuric acid, then on treatment of the reaction mass with water we isolated 29% of unreacted dimedon and 42% of the sodium dimedon sulfonate. The dimedon is formed as a result of hydrolysis of dimedon hydrogen sulfate.

b) Sulfonation of dimedon with 86% sulfuric acid. We heated 0.7 ml of 86% sulfuric acid, 1.3 ml of acetic anhydride, 4 ml of 1,2-dichloroethane, and 1.4 g of dimedon on a water bath for 30 min. The reaction mass was cooled to 0°. After several hours the precipitate was filtered off and washed with 1,2-dichloroethane. We obtained

1.6 g (67.5%) of dimedon hydrogen sulfate (II). M.p. 140-141°. From the filtrate after treatment with water and salting out with sodium chloride, we obtained 0.6 g (21.5%) of sodium dimedon sulfonate. If in the sulfonation we used 2 moles of acetic anhydride per 1 mole of 86% sulfuric acid, we obtained a 91.5% yield of dimedon sulfonic acid, and dimedon hydrogen sulfate was not formed.

c) Sulfonation of dimedon with sulfuric anhydride. Into a suspension of 1.4 g of dimedon in 10 ml of anhydrous chloroform we passed sulfuric anhydride. The dimedon dissolved and the reaction mass grew warm and assumed a brownish color. After absorption of 0.8 g of sulfuric anhydride dimedon sulfonic acid precipitated and passage of SO_3 was stopped. We filtered off 0.35 g of dimedon sulfonic acid. The filtrate was washed with water. The water solution was neutralized with sodium carbonate to pH 5 and salted out with sodium chloride. We obtained 2.1 g (92%) of sodium dimedon sulfonate.

If passage of sulfuric anhydride was continued even after the appearance of the precipitate, the latter dissolved and a homogeneous solution was obtained. When 1.7 g of sulfuric anhydride had entered the reaction mixture, a white, very hygroscopic substance precipitated. The latter dissolved in water and after salting out with sodium chloride gave 2.4 g (88%) of sodium dimedon sulfonate. From the filtrate we precipitated 2.4 g of barium sulfate. This means that the precipitate contained two molecules of sulfuric anhydride per molecule of dimedon. The structure of this compound remains undetermined.

Hydrolysis of dimedon hydrogen sulfate. On addition of 10 ml of water to 1.2 g of dimedon hydrogen sulfate, it was converted into dimedon. Barium chloride precipitated the sulfate ion from the filtrate. We obtained 1.14 g (98%) barium sulfate. Dimedon was formed with a yield of 88%. Dimedon was also obtained in the reaction of dimedon hydrogen sulfate with anhydrous sodium acetate in yield of 90%, and from anhydrous sodium carbonate with a yield of 93%.

Dimedon ethyl ether. We heated in a flask with a reflux condenser, for 10 min, 2.38 g (0.01 mole) of dimedon hydrogen sulfate and 5 ml of anhydrous ethanol at 40°. The reaction product was poured into a solution of sodium carbonate. It was extracted with ether and the ether layer was washed several times with water. The ether was distilled off leaving an oily product which crystallized on standing in a desiccator. Yield 1.4 g (82%), m.p. 56-57° (from ligroin) (60° [18]). We could not obtain the phenyl ether in this way.

Reaction of dimedon hydrogen sulfate with acetic anhydride. Five ml of acetic anhydride was added to 2.38 g of dimedon hydrogen sulfate. A small amount of heating occurred and a homogeneous mass formed (if the reaction did not begin, it was heated somewhat on a water bath), and on cooling this crystallized. We obtained 1.7 g (77%) of dimedon sulfonic acid. M.p. 109°. It gave no depression of the melting point with dimedon sulfonic acid obtained by other methods.

Thermal decomposition of dimedon sulfonic acid. A mixture of 0.55 g of dimedon sulfonic acid and 4 ml of anhydrous toluene was carefully heated on an oil bath to 102-103°. The sulfonic acid melted. On cooling, the mass set. It was filtered, washed with anhydrous toluene, and gave 0.54 g (90.6%) of dimedon hydrogen sulfate. M.p. 139-140°. A sample mixed with the hydrogen sulfate obtained by direct sulfonation of dimedon gave no depression of the melting point.

Hydrolysis of dimedon sulfonic acid by concentrated hydrochloric acid. We heated 1.5 g of dimedon sulfonic acid in 5 ml of concentrated hydrochloric acid and allowed it to stand for 20 hr. It was diluted with water and neutralized with sodium carbonate to pH 5. The precipitated dimedon (0.23 g) was filtered and the sulfate ion was precipitated with barium chloride. We obtained 0.49 g (31%) of barium sulfate. On boiling with concentrated hydrochloric acid hydrolysis occurred completely in 5-8 hr.

Infrared spectra were photographed in a monochromatic infrared spectrophotometer IKS-12 with a prism of NaCl. The substances were photographed in the form of a suspension in vaseline oil.

SUMMARY

1. We have studied the course of the reaction of sulfonation of dimedon by sulfuric acid of different concentrations in the presence of acetic anhydride.

2. With insufficient acetic anhydride a new substance is obtained which is assigned the structure of dimedon hydrogen sulfate.

3. The structur s of the sodium and ammonium salts of dimedon sulfonic acid have been confirmed by their absorption spectra in the infrared.

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•Original Russian pagination. See C. B. translation.

STUDIES IN THE FIELD OF QUINONES

XXXI. THE SYNTHESIS OF TETRAHYDRO-1,4-ENDOMETHYLENEANTHRAQUINONE

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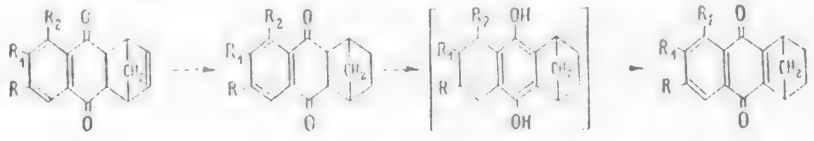
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1911-1914, June, 1960
Original article submitted June 25, 1959

In attempts to isomerize the adducts of p-quinones with cyclopentadiene into hydroquinones, they underwent polymerization. However, after reduction of the double bond in the adducts of 1,4-naphthoquinones with cyclopentadiene, they were easily isomerized into the substituted hydroquinone. The substituted hydroquinones without isolation were oxidized into tetrahydro-1,4-endomethyleneanthraquinones.



(I) R, R_1, R_2 = H;
(II) R, R_1 = H; R_2 = CH_3;
(III) R, R_2 = H; R_1 = CH_3;
(IV) R, R_1 = CH_3; R_2 = H;
(V) R, R_1, R_2 = H;
(VI) R, R_1 = H; R_2 = CH_3;
(VII) R, R_2 = H; R_1 = CH_3;
(VIII) R, R_1 = CH_3; R_2 = H;
(IX) R, R_1, R_2 = H;
(X) R, R_1 = H; R_2 = CH_3;
(XI) R, R_2 = H; R_1 = CH_3;
(XII) R, R_1 = CH_3; R_2 = H.

The isomerization of the hydrogenated adducts and oxidation of the intermediate hydroquinones into quinones was carried out under conditions analogous to those described in our work [1-3]. Formation of the adducts of naphthoquinones with cyclopentadiene occurred best by carrying out the reaction in acetic acid or in methanol with addition of acetic acid.

EXPERIMENTAL

5-Methyl-1,4,4a,9a-tetrahydro-1,4-endomethyleneanthraquinone (II). To a solution of 25.9 g of 5-methyl-1,4-naphthoquinone in 50 ml of methanol we added 2 ml of acetic acid and 12.8 g of cyclopentadiene. The reaction mixture stood for 30 min and then was diluted with water and cooled. The resulting crystalline mass was filtered and washed with a small amount of a mixture of ether and ligroin (3 : 2). This freed the adduct from tarry impurities. The yield of adduct (II) was 28.7 g (83%), m.p. 59-59.5° (from ether).

Found %: C 80.44; H 5.90. $C_{16}H_{14}O_2$. Calculated %: C 80.64; H 5.92.

The other adducts (I, III, IV) were obtained under analogous conditions (Table 1).

5-Methyl-1,2,3,4,4a,9a-hexahydro-1,4-endomethyleneanthraquinone (VI). We dissolved 41.2 g of adduct (II) in 160 ml of alcohol in a hydrogenation vessel. To the resulting solution we added 18 ml of a sample of Raney nickel in alcohol, and then hydrogenated at 58-60°, adding the stoichiometric amount of hydrogen. The alcohol solution was diluted with water and the precipitate of hydrogenated adduct (VI) was filtered, washed with a small amount of methanol, and dried. Yield of (VI) 33.3 g (80%), m.p. 85.5-86° (from ligroin).

TABLE 1

Obtaining Adducts

Starting naphthoquinone	Amount of naphthoquinone (g)	Cyclopentadiene (g)	CH_3OH (ml)	CH_2COOH (ml)	Resulting adduct	Yield, %	M.p.	Found, %		Calc., %	
								C	H	C	H
1,4-Naphthoquinone	63.2	28.8	200	10	1,4,4a,9a-tetrahydro-1,4-endomethyleneanthraquinone (I)	89	108—109° *	—	—	—	—
5-Methyl-1,4-naphthoquinone	25.9	12.8	50	2	5-methyl-1,4,4a,9a,-tetrahydro-1,4-endomethyleneanthraquinone (II)	83	59—59.5	80.44	5.90	80.64	5.92
6-Methyl-1,4-naphthoquinone	51.7	28.2	—	52	6-methyl-1,4,4a,9a-tetrahydro-1,4-endomethyleneanthraquinone (III)	87	121—121.5	80.37	5.91	80.64	5.92
6,7-Dimethyl-1,4-naphthoquinone	16.8	7.2	—	70	6,7-dimethyl-1,4,4a,9a-tetrahydro-1,4-endomethyleneanthraquinone (IV)	98	151—152	80.83	6.43	80.92	6.39

*According to [4], m.p. 115°

TABLE 2

Hydrogenation of the Adducts

Starting adduct	Amt. of adduct, g	Raney Ni (in ml of sample)	Temp.	C_2H_5OH ml	Benzene ml	Hydrogenated adduct	Yield %	M.p.	Found, %		Calc., %	
									C	H	C	H
(I)	9	6	58—60°	100	—	1,2,3,4,4a,9a-Hexahydro-1,4-endomethyleneanthraquinone (V)	85	113.5—114.5° *	—	—	—	—
(II)	41.2	18	58—60	160	—	5-Methyl-1,2,3,4,4a,9a-hexahydro-1,4-endomethyleneanthraquinone (VI)	80	85.5—86	80.17	6.71	79.97	6.71
(III)	58.4	22	58—60	50	300	6-Methyl-1,2,3,4,4a,9a-hexahydro-1,4-endomethyleneanthraquinone (VII)	64	120—120.5	79.93	6.69	79.97	6.71
(IV)	18	14	58—60	50	130	6,7-Dimethyl-1,2,3,4,4a,9a-hexahydro-1,4-endomethyleneanthraquinone (VIII)	61	131—132	80.54	7.03	80.28	7.13

*According to [5], m.p. 117°.

TABLE 3

Obtaining Quinones

Hydrogenated adduct	Amt. of adduct, g	CH_3COOH for isomerization of adduct ml	Oxidizing mixture				Resulting quinone	Yield, %	M.p.	Found, %		Calc., %	
			$KBrO_3$, g	1 N H_2SO_4, ml	water ml	CH_3COOH, ml				C	H	C	H
(V)	2.4	5	1.2	2	12	15	1,4-Dihydro-1,4-endomethyleneanthraquinone (IX)	97	133.5—134°	80.44	5.47	80.33	5.39
(VI)	4	8	0.8	1	8	12	5-Methyl-1,4-dihydro-1,4-endomethyleneanthraquinone (X)	73	104—105	80.67	5.91	80.64	5.92
(VII)	37.6	80	8.8	14	90	—	6-Methyl-1,4-dihydro-1,4-endomethyleneanthraquinone (XI)	79	153—153.5	80.61	6.04	80.64	5.92
(VIII)	11.1	35	2.5	4	26	25	6,7-Dimethyl-1,4-dihydro-1,4-endomethyleneanthraquinone (XII)	74	171.5—172	81.06	6.51	80.92	6.39

Found %: C 80.17; H 6.71. $C_{16}H_{16}O_2$. Calculated %: C 79.97; H 6.71.

Hydrogenation of the other adducts was carried out in an analogous manner (Table 2).

5-Methyl-1,4-dihydro-1,4-endomethyleneanthraquinone (X). We boiled 4 g of hydrogenated adduct (VI) in 8 ml of acetic acid for 1.5 hr. To the resulting reaction mixture we added 12 ml of acetic acid, 1 ml of 1 N sulfuric acid, and a solution of 0.8 g of potassium bromate in water. After shaking and short heating, the reaction solution became yellow colored. It was cooled and the precipitating crystals of quinone (X) were filtered and dried. Yield of (X) 2.9 g (73%), m.p. 104-105° (from methanol).

Found %: C 80.67; H 5.91. $C_{16}H_{14}O_2$. Calculated %: C 80.65; H 5.92.

The other quinones (IX, XI, XII) were obtained in an analogous manner (Table 3).

SUMMARY

By the method worked out earlier we have obtained from α-naphthoquinones and cyclopentadiene a series of substituted tetrahydroanthraquinones.

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STUDIES IN THE FIELD OF QUINONES

XXXII. THE SYNTHESIS OF SUBSTITUTED 2,5-BIS(AMINO)-1,4-BENZOQUINONES AND 2-AMINO-1,4-NAPHTHOQUINONES

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1914-1918, June, 1960
Original article submitted June 25, 1959

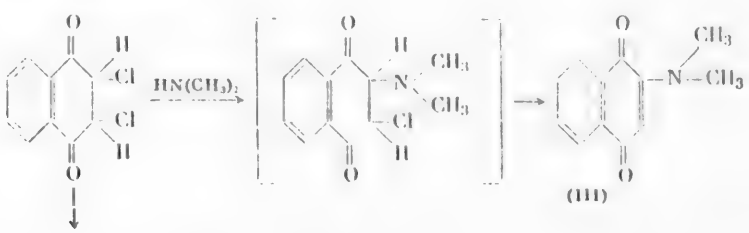
Substituted aminoquinones have recently attracted considerable interest. Some compounds of this class are used for treating cancer, since they can resolve tumors [1-4], and have bacteriocidal [5] and amebocidal activity [6].

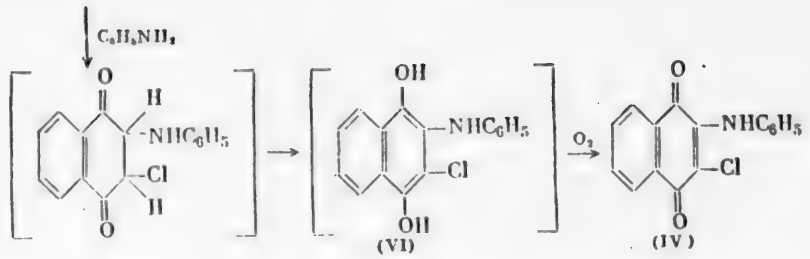
2,5-bis(Dimethylamino)-1,4-benzoquinone and 2-dimethylamino-1,4-naphthoquinone, as one of our investigations has shown [7], are suitable model compounds for studying electrophilic substituents in a series of reactions of p-quinones.

By the methods described in a number of studies [8-12] aminoquinones with substituted alkyl groups on the nitrogen are obtained in low yields. Only recently, in works published by American scientists [13, 14], has it become possible to obtain a number of substituted aminoquinones by a method of oxidative amination of p-benzoquinone with nearly quantitative yields.

In the present study the method of oxidative amination has been used for the synthesis of 2,5-bis(dimethylamino)-p-benzoquinone (I), 2,5-bis(hexamethyleneamino)-p-benzoquinone (II), and 2-dimethylamino-1,4-naphthoquinone (III). As the starting compound for preparing 2,5-bis(dimethylamino)-p-benzoquinone (I), in distinction from other investigators [13, 14], we used hydroquinone instead of p-benzoquinone.

We also succeeded in carrying out for the first time the synthesis of some substituted naphthoquinones by the action of amines on the products of addition of chlorine and bromine to 1,4-naphthoquinone: 1,4-naphthoquinone dichloride and 1,4-naphthoquinone dibromide. It is interesting that in the reaction of 1,4-naphthoquinone dichloride with dimethylamine we obtained 2-dimethylamino-1,4-naphthoquinone (III), and when we carried out the reaction under the same conditions with aniline we obtained 2-chloro-3-anilino-1,4-naphthoquinone (IV) and 2-bromo-3-anilino-1,4-naphthoquinone (V). The intermediate hydroquinone (VI) was oxidized by oxygen of the air into quinone (IV).

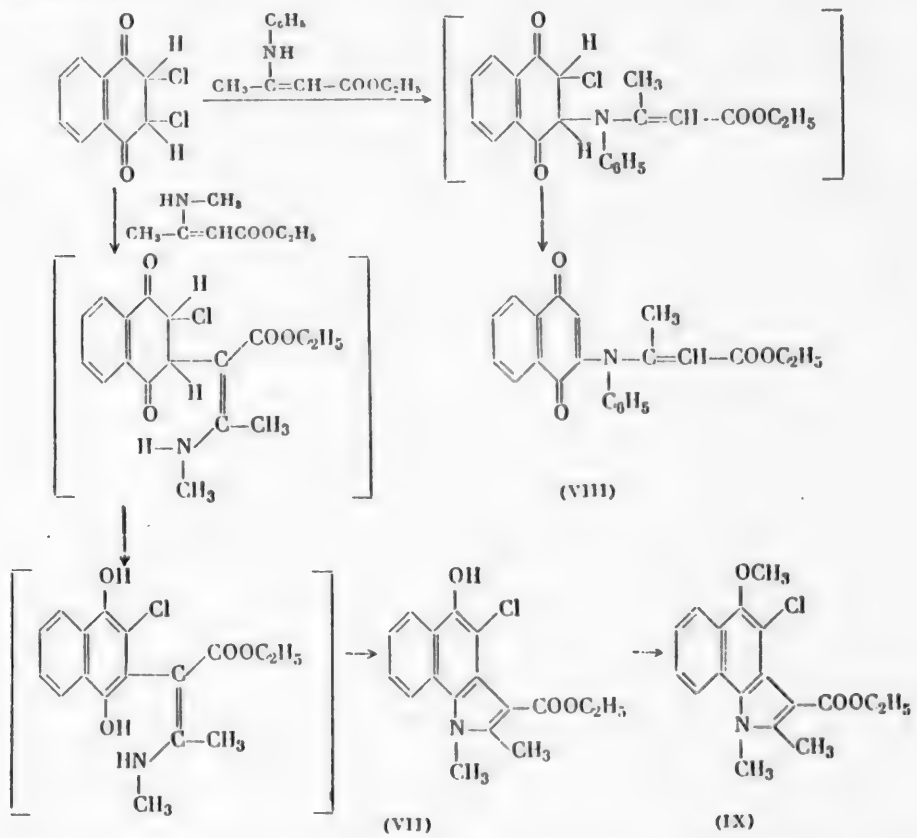




Another scheme for the reaction which suggests the formation as an intermediate compound of chloro-1,4-naphthoquinone or 2,3-dichloro-1,4-naphthoquinone is easily rejected since the replacement of chlorine in a halogen substituted 1,4-naphthoquinone by a dimethylamine or aniline residue takes place under more severe conditions (heating for several hours). The reaction of 1,4-naphthoquinone dichloride with amines is complete after short heating (20 min) in methanol.

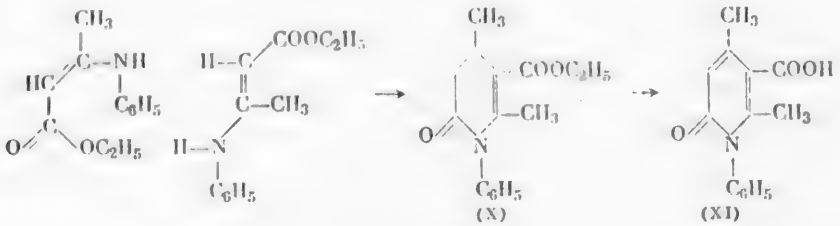
The reaction of esters of β-aminocrotonic acid, substituted on the nitrogen, with 1,4-naphthoquinone dichloride, depending on the character of the radical bound to the nitrogen, takes place in different directions: the reaction of ethyl N-methyl-β-aminocrotonate with 1,4-naphthoquinone dichloride leads to the production of the benzindole (VII), while carrying out the reaction with ethyl N-phenyl-β-aminocrotonate gives N-phenyl-N-naphthoquinone-β-aminocrotonic ester (VIII).

The 5-hydroxybenzindole (VII) which is formed is converted by the action of dimethylsulfate in alkali to 5-methoxybenzindole (IX).



The condensation of 1,4-naphthoquinone dichloride with esters of β-aminocrotonic acid which occurs in the presence of acid catalysts (H_2SO_4, H_3PO_4) can lead to the formation of side products when it is varied from the optimum conditions. For example, when the reaction is carried out under different conditions we isolated a derivative of α-pyridone (X). We obtained this product in good yield by the intermolecular condensation of

N-phenyl-β-aminocrotonic ester in the presence of hydrogen chloride. 1-Phenyl-4,6-dimethyl-5-carbethoxy-2-pyridone (X) in alkaline hydrolysis is converted to 1-phenyl-4,6-dimethyl-5-carboxy-2-pyridone (XI).



(X) (XI)

EXPERIMENTAL

2,5-bis(Dimethylamino)-1,4-benzoquinone (I). To a solution of the copper complex obtained from 40 g of copper acetate and 45 g of dimethylamine in 600 ml of methanol was added with cooling a solution of 22 g of hydroquinone in 400 ml of methanol. Air was passed through the reaction mixture at room temperature with stirring for 1-1.5 hr; the reaction mixture stood overnight in a refrigerator. The crystals which separated were filtered off. For purification from cuprous oxide, the crystals of quinone (I) were placed in a Soxhlet apparatus and extracted with 200 ml of methanol. The methanol solution was cooled in a refrigerator, the separated crystals of quinone (I) were removed and dried in a vacuum desiccator over phosphoric anhydride. Yield of (I) 38.5 g (quantitative), m.p. 171-172°. According to the literature [14]: m.p. 170°.

2,5-bis(Hexamethyleneamino)-p-benzoquinone (II). To a solution of the copper complex prepared from 7.5 g of hexamethyleneamine and 2.5 g of copper acetate in 150 ml of methanol was added a solution of 5.4 g of p-benzoquinone in 100 ml of methanol. Oxidation and isolation of the substance was carried out under the conditions of the previous experiment. Yield of (II) 7.9 g (78.5%), m.p. 157° (from methanol).

Found %: C 71.78, 71.73; H 9.01, 8.89; N 9.24, 9.36. $C_{18}H_{26}O_2N_2$. Calculated %: C 71.49; H 8.67; N 9.26.

2-Dimethylamino-1,4-naphthoquinone (III). We mixed a solution of the copper complex obtained from 20 g of copper acetate and 15.5 g of dimethylamine in 300 ml of methanol with a suspension of 15.8 g of 1,4-naphthoquinone in 200 ml of methanol. Reaction and isolation of the substance were carried out under the conditions of obtaining 2,5-bis(dimethylamino)-1,4-benzoquinone (I). Yield of (III) 20 g (quantitative), m.p. 121.5-122.5°; according to the literature [15], m.p. 118°.

2-Dimethylamino-1,4-naphthoquinone (III) from 1,4-naphthoquinone dichloride. A solution of 2.3 g of 1,4-naphthoquinone dichloride in 50 ml of methanol was saturated with 2.3 g of dimethylamine with cooling. The reaction mixture was boiled for 20 min under reflux on the water bath. The hot, dark-red solution was filtered. Twice the volume of water was added to the filtrate. The crystals of (III) which precipitated were filtered off and dried. Yield of (III) 1.9 g (83.4%), m.p. 120-121° (from benzene); according to the results of [15], m.p. 118°.

2-Chloro-3-anilino-1,4-naphthoquinone (IV). The reaction mixture from 2.29 g of 1,4-naphthoquinone dichloride, 1.86 g aniline and 50 ml of methanol was heated on a water bath for 20 min. The crystals which precipitated on cooling were recrystallized from benzene. The aniline hydrochloride, insoluble in benzene, was then separated. Yield of (IV) 2.2 g (77.6%), m.p. 203°; according to [16], m.p. 202-203°.

2-Bromo-3-anilino-1,4-naphthoquinone (V). For the experiment we took 3.18 g of 1,4-naphthoquinone dibromide, 1.86 g of aniline, and 25 ml of methanol. The reaction and isolation of quinone (V) were carried out under the conditions of the previous experiment. Yield of (V) 1.1 g (33.5%), m.p. 189-190° (from benzene); according to [17], m.p. 190°.

1,2-Dimethyl-3-carbethoxy-4-chloro-5-hydroxybenzindole (VII). We mixed 2.9 g of N-methyl-β-aminocrotonic ester, 2.3 g of 1,4-naphthoquinone dichloride and 25 ml of methanol. To this mixture of substances we added 2 drops of 85% phosphoric acid. The reaction mixture was boiled 20 min on a water bath under reflux. The hot solution was filtered from the precipitate. On standing, a further precipitate appeared in the filtrate. It was washed with benzene, recrystallized from methanol, and air dried. Yield of (VII) 1.13 g (35.5%), m.p. 163° (from methanol).

Found %: C 61.56, 61.70; H 5.69, 5.61. $C_{17}H_{16}O_3NCl \cdot CH_3OH$. Calculated %: C 61.80; H 5.72.

1,2-Dimethyl-3-carbethoxy-4-chloro-5-methoxybenzindole (IX). We mixed 3.54 g of hydroxybenzindole (VII) with 3 ml of dioxane, 5 g of dimethyl sulfate, and 10 ml of 2 N sodium hydroxide. The reaction mixture was shaken for 30 min at room temperature. The precipitate was filtered and washed with water. Yield of (IX) 3.63 g (quantitative), m.p. 136° (from methanol).

Found %: C 64.86, 64.67; H 5.67, 5.44. $C_{18}H_{18}O_3NCl$. Calculated %: C 65.13; H 5.43.

N-Phenyl-N-naphthoquinone-β-aminocrotonic ester (VIII). We mixed 2.3 g of 1,4-naphthoquinone dichloride and 4.1 g of N-phenyl-β-aminocrotonic ester in 25 ml of methanol. To the resulting mixture we added 2 drops of concentrated sulfuric acid in 2 ml of acetic acid. The reaction mixture was boiled for 20 min on a water bath. The hot solution was filtered. From the filtrate after partial evaporation of the solvent we obtained red crystals with m.p. 197-199°. Yield of (VIII) 1.25 g (34.6%). After three recrystallizations from methanol the m.p. was 218-219°.

Found %: C 73.25, 73.10; H 5.03, 5.12. $C_{22}H_{19}O_4N$. Calculated %: C 73.13; H 5.26.

1-Phenyl-4,6-dimethyl-3-carbethoxy-2-pyridone (X). We dissolved 10.4 g of N-phenyl-β-aminocrotonic ester in 100 ml of dichloroethane and saturated the resulting solution with hydrogen chloride. Then we boiled the reaction mixture one hour under reflux. The precipitate of aniline hydrochloride was filtered and washed on the filter with benzene. From the filtrate, which contained benzene and dichloroethane, we distilled most of the solvent, and again separated the precipitate of aniline salt. After removal of the solvent from the filtrate in a vacuum we obtained crystals of pyridone (X). Yield 3.5 g (50.9%), m.p. 92-93° (from methanol).

Found %: C 70.67, 70.69; H 6.34, 6.57; N 5.22, 5.16. $C_{16}H_{17}O_3N$. Calculated %: C 70.83; H 6.32; N 5.16.

1-Phenyl-4,6-dimethyl-5-carboxy-2-pyridone (XI). We boiled 7.8 g of ester (X) with a solution of 7 g of potassium hydroxide in 75 ml of alcohol; then most of the solvent was distilled off. The residue was dissolved in water and precipitated with 2 N hydrochloric acid. Yield of (XI) 4.8 g (69.5%), m.p. 123-124° (after three recrystallizations from methanol).

Found %: C 68.99, 69.13; H 5.41, 5.46; N 5.44, 5.63. $C_{14}H_{13}O_3N$. Calculated %: C 69.12; H 5.39; N 5.76.

SUMMARY

1. By the method of oxidative amination we have carried out the synthesis of 2,5-bis(dimethylamino)-p-benzoquinone (from hydroquinone), 2,5-bis(hexamethyleneamino)-p-benzoquinone, and 2-dimethylamino-1,4-naphthoquinone.

2. We have studied for the first time the reactions of 1,4-naphthoquinone dichloride and 1,4-naphthoquinone dibromide with amines; we have obtained: 2-dimethylamino-1,4-naphthoquinone, 2-chloro-3-anilino-1,4-naphthoquinone, and 2-bromo-3-anilino-1,4-naphthoquinone. In the reaction of 1,4-naphthoquinone dichloride with N-methyl-β-aminocrotonic ester and N-phenyl-β-aminocrotonic ester we have obtained 1,2-dimethyl-3-carbethoxy-4-chloro-5-hydroxybenzindole and N-phenyl-N-naphthoquinone-β-aminocrotonic ester.

3. Intermolecular condensation of N-phenyl-β-aminocrotonic ester gives 1-phenyl-4,6-dimethyl-5-carbethoxy-2-pyridone, which is formed as a side product when the reaction of 1,4-naphthoquinone dichloride with N-phenyl-β-aminocrotonic ester is varied from the optimum conditions.

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HERBICIDES AND PLANT GROWTH REGULATORS

XXXV. SYNTHESIS OF SOME TRIPHENYLPHENOXYALKYL PHOSPHONIUM SALTS

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1918-1921, June, 1960
Original article submitted June 4, 1959

In recent years, organic phosphorus compounds have found continually wider use in agriculture as materials for combating harmful plants [1, 2] and very recently for suppressing weeds, [3-7] and as defoliants [8-11]. Because of their ability to travel in the plant, the organic phosphorus herbicides and defoliants differ in the rapidity of their action, which is of very great interest.

In connection with the systematic study of the herbicidal properties of different classes of organic compounds, we have undertaken the synthesis of study of a number of organic compounds of phosphorus. To begin with, we have synthesized compounds of general formula (I), from which, by analogy with the corresponding salts of amines, we may expect physiological activity toward plants.

$$(C_6H_5)_3P(X)(CH_2)_nOAr$$
(I)

The synthesis of these compounds was carried out by reacting triphenyl phosphine with the corresponding aryloxyalkyl halides. The reaction was run either by heating a mixture of equimolecular amounts of the starting compounds on a metal bath at 120-150°, or by boiling a solution of them in xylene or toluene. It should be noted that formation of phosphonium salts occurs quite slowly and obtaining the best yields requires a very long heating of the reaction mixtures. It is interesting to note that triphenyl phosphine reacts most easily with chloromethylaryl ethers, and with the greatest difficulty with aryloxypropyl halides and butyl halides, and in general it is not possible to obtain under our conditions salts of quaternary phosphonium bases from triphenyl phosphine and aryloxyethyl halides. The compounds which we synthesized and which are not described in the literature are given in Table 1.

In order to determine the herbicidal action, wheat and radish seeds were soaked in 0.001-0.1% aqueous solutions of the preparations for 24 hr and then their germination was determined. As a result of these experiments it was shown that 2,4,5-trichlorophenoxymethyltriphenyl phosphonium chloride, 2,4,5-trichlorophenoxybutyltriphenyl phosphonium bromide, and 4-chlorophenoxybutyltriphenyl phosphonium bromide in concentrations of 0.1% strongly hindered the growth of seeds, and 2,4,5-trichlorophenoxypropyltriphenyl phosphonium chloride at the same concentration was practically inactive.

EXPERIMENTAL

Starting compounds. Aryloxychloromethanes were obtained by the action of phosphorus oxychloride on the sodium aryloxymethane sulfonates [12], aryloxyethyl halides from the corresponding aryloxyethanols [13, 14] by the action on them of thionyl chloride or hydrogen bromide, and the aryloxypropyl and aryloxybutyl halides, by the reaction of alkane dihalides with the corresponding phenolates of the alkali metals [15]. Some of these compounds have not been described in the literature. Those which have not are given in Table 2.

TABLE 1

Properties of Triphenylaryloxyalkyl Phosphonium Halides

Formula	Yield, %	M.p.	% P		% Cl'	
			found	calc.	found	calc.
$C_6H_5OCH_2P(C_6H_5)_3Cl$	65	195—197°	7.65, 7.58	7.67	8.92, 8.88	8.76
$4\text{-}ClC_6H_4OCH_2P(C_6H_5)_3Cl$	54	198—204	7.04, 6.92	7.06	8.10, 8.23	8.07
$2,4,5\text{-}Cl_3C_6H_2OCH_2P(C_6H_5)_3Cl$	47	197—199	5.80, 5.79	6.11	7.14, 7.08	6.98
$C_6H_5SCH_2P(C_6H_5)_3Cl$	35	210—212	—	—	8.62, 8.83	8.42
$C_6H_5OCH_2CH_2CH_2P(C_6H_5)_3Cl$	62	171.5—172.5	6.92, 6.87	7.17	8.32, 8.24	8.19
$4\text{-}ClC_6H_4OCH_2CH_2CH_2P(C_6H_5)_3Cl$	50	129—134	6.40, 6.39	6.64	7.86, 7.85	7.59
$2,4,5\text{-}Cl_3C_6H_2OCH_2CH_2CH_2P(C_6H_5)_3Cl$	13	230—238	5.72, 5.56	5.79	6.45, 6.46	6.61
$C_6H_5OCH_2CH_2CH_2P(C_6H_5)_3Br$	85	177—178	6.15, 6.49	6.50	16.94, 17.04	16.74 (Br)
$4\text{-}ClC_6H_4OCH_2CH_2CH_2P(C_6H_5)_3Br$	82	123—126	5.96, 5.75	6.06	15.17, 15.48	15.61 (Br)
$C_6H_5OCH_2CH_2CH_2CH_2P(C_6H_5)_3Br$	79	178—179	6.05, 6.19	6.32	15.94, 16.15	16.26 (Br)
$4\text{-}ClC_6H_4OCH_2CH_2CH_2CH_2P(C_6H_5)_3Br$	83	171—173	5.82, 5.98	5.90	15.28, 15.51	15.19 (Br)
$2,4,5\text{-}Cl_3C_6H_2OCH_2CH_2CH_2CH_2P(C_6H_5)_3Br$	87	150—153	5.13, 5.18	5.22	13.09, 12.99	13.14 (Br)

TABLE 2

Properties of Aryloxyalkyl Halides

Formula	Yield, %	Temperature		Percent halogen	
		of melting	of boiling (pressure in mm)	found	calc.
$4\text{-}ClC_6H_4OCH_2CH_2Cl$ *	84	41°	254—256° (760)	36.98, 37.39	37.12
$2,4\text{-}Cl_2C_6H_3OCH_2CH_2Cl$ *	83	31	276—278 (760)	47.59, 47.37	47.17
$2,4,5\text{-}Cl_3C_6H_2OCH_2CH_2Cl$	46	54	300—302 (760)	54.31, 54.40	54.56
$4\text{-}ClC_6H_4OCH_2CH_2CH_2Cl$ **	66	—	145—147 (10)	51.10, 51.14	51.77
$2,4,5\text{-}Cl_3C_6H_2OCH_2CH_2CH_2Cl$	69	45	180—182 (8)		
$4\text{-}ClC_6H_4OCH_2CH_2CH_2CH_2Br$	70	34	166 (6)		
$2,4,5\text{-}Cl_3C_6H_2OCH_2CH_2CH_2CH_2Br$ ***	66	—	192—194 (5)	23.61, 23.74 (Br); 31.38, 31.55 (Cl)	24.04 (Br); 31.99 (Cl)

* Cf. [16].

** d^{20}_4 1.252, $n^{20}D$ 1.5415, MR_D 51.51; calc. 51.54.

*** d^{20}_4 1.5862, $n^{20}D$ 1.5775, MR_D 69.50; calc. 68.79.

Reaction of aryloxyalkyl halides with triphenyl phosphine. In a flask with a reflux condenser was placed a toluene solution of equimolecular amounts of the starting substances and the solution was boiled for 20-30 hr. The precipitate which separated was filtered off and washed with toluene and ether. After removal of the ether in most cases the tetra substituted phosphonium salt was obtained in an analytically pure form. In some cases the salt was recrystallized from acetone for purification. It is interesting to observe that most of the reaction in almost all cases occurred in the first hours, and with further heating the yield increased by only 10-15%. Thus, for example, in the reaction of triphenylphosphine with chloromethylphenyl ether, in the first 23 hr of heating the toluene solution of the components, 56% of the theoretical of the quaternary salt separated, and in the last 108 hr, only 9%.

We also obtained some triphenylaryloxyalkyl phosphonium salts by heating equimolecular amounts of the starting substances in a flask with a reflux condenser on a metal bath at 150° without a solvent. The yield of triphenylaryloxyalkyl phosphonium salt in this case was somewhat higher, but the product was less pure with a melting point 3-6° lower than when a solvent was used. However, the duration of the reaction without a solvent was substantially less.

None of our compounds have been described in the literature; they are white, crystalline substances with comparatively high melting points, poorly soluble in water and most organic solvents. The compounds which we have synthesized and their properties are given in Table 1.

SUMMARY

In order to study the herbicidal properties we have synthesized from triphenylphosphine and aryloxyalkyl halides a number of undescribed triphenylaryloxyalkylphosphonium salts. Study of these compounds on sprouting wheat and radish seeds showed that their physiological activity was small.

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THE CYCLOALKYLATION OF AROMATIC COMPOUNDS

XVI. THE REACTION OF 1-PHENYL-2-METHYLCYCLOHEXANOL WITH BENZENE

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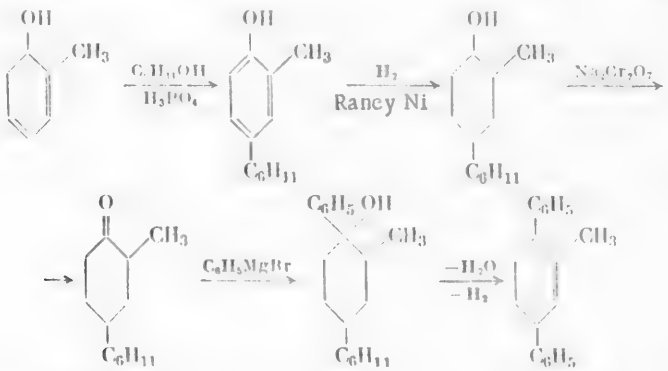
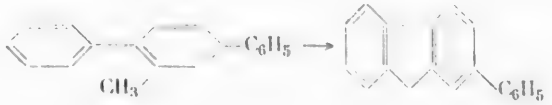
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1921-1926, June, 1960
Original article submitted June 29, 1959

In one of the previous studies [1] it was shown that the reaction of 1-phenyl-4-methylcyclohexanol with benzene in the presence of aluminum chloride goes in two directions with formation of alkylation products and products of reduction, and that both types of reaction are accompanied by isomerization of the alcohol radical. Continuing this work we have studied the reaction of 1-phenyl-2-methylcyclohexanol with benzene in the presence of aluminum chloride. Here, besides the alkylation products (a mixture of methyldiphenylcyclohexanes)we have also obtained reduction products (a mixture of methylphenylcyclohexanes) with about the same yield. The reaction in the presence of aluminum bromide gave preferentially methylphenylcyclohexanes and only a small amount of methyldiphenylcyclohexanes. This result was unexpected, since in the reaction of 1-phenylcyclohexanol with benzene, the reverse relation was found [2].

The alkylation product is a complex mixture from which we isolated two individual crystalline substances, but the main mass remained liquid even when cooled to –60°. One of the crystalline substances (with m.p. 97°) was shown to be 1-methyl-2,5-diphenylcyclohexane. When it was dehydrogenated it gave 1-methyl-2,5-diphenylbenzene (with m.p. 91-92°) whose structure was shown by synthesis according to the scheme

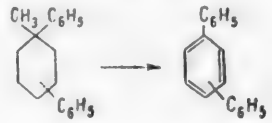


The synthesized hydrocarbon melted at 91-92° and its mixture with the dehydrogenated hydrocarbon also melted at 91-92°. Both samples of 1-methyl-2,5-diphenylbenzene on further dehydrogenation gave 2-phenylfluorene, identified by mixed melting point with 2-phenylfluorene obtained in dehydrogenation of 2-cyclohexylfluorene [3].



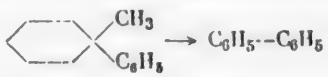
The structure of the second crystalline methyldiphenylcyclohexane (m.p. 113°) was not established. When boiled for a long time with platinized carbon it did not change at all; reaction occurred only at temperatures above 400° in a sealed tube, but under these conditions after four hours heating most of the hydrocarbon was recovered unchanged. The difficulty in dehydrogenation shows the presence of a quaternary carbon atom.

The liquid alkylation product was a mixture of several hydrocarbons. Among the products of its dehydrogenation were found 1-methyl-2,5-diphenylbenzene, 2-phenylfluorene, m- and p-terphenyl. The first two substances were formed from 1-methyl-2,5-diphenylcyclohexane which had not been fully removed from the mixture, and the m- and p-terphenyl could be obtained only from dehydrogenation of 1,3- and 1,4-diphenyl-1-methylcyclohexane with splitting off of the methyl group from the quaternary atom of carbon.



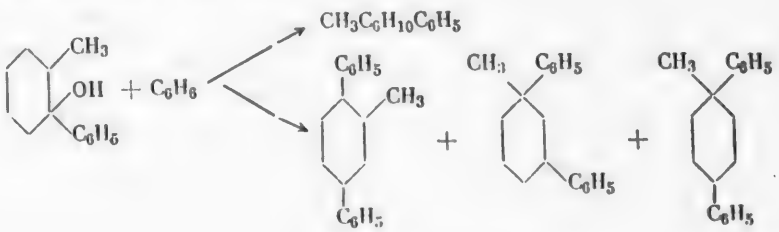
The substance with m.p. 113° is evidently one of these hydrocarbons.

The product of reduction consisted of a mixture of methylphenylcyclohexanes, in which was a considerable amount of the 1,1-isomer, as was shown by obtaining diphenyl in dehydrogenation.



Besides the diphenyl we obtained fluorene and liquid hydrocarbons, evidently methyldiphenyls.

Thus we have shown that the reaction of 1-phenyl-2-methylcyclohexanol with benzene in the presence of aluminum chloride goes according to the scheme:



EXPERIMENTAL

1-Phenyl-2-methylcyclohexanol was obtained from phenylmagnesium bromide and 2-methylcyclohexanone [4]. Yield 83%, b.p. 105-108° (2 mm), $n^{20}D$ 1.5366. Contains traces of olefins.

Reaction of 1-phenyl-2-methylcyclohexanol with benzene. To 19.0 g (0.1 mole) of 1-phenyl-2-methylcyclohexanol dissolved in 200 ml (2.3 -mole) of benzene was added in the course of one hour, with stirring, 13.4 g (0.1 mole) of ground aluminum chloride. The mixture stood until the next day and then was heated for two hours on a water bath, first at 50-60° and then to boiling. After the usual treatment we obtained 6.6-8.0 g (38-46%) of a methylphenylcyclohexane fraction with b.p. 110-120° (11 mm), and 9.6-10.6 g (38-42.4%) of a methyldiphenylcyclohexane fraction with b.p. 150-170° (3 mm) or 195-210° (15 mm). With 8.0 g (0.06 mole) of aluminum chloride the yield of methylphenylcyclohexanes was the same, but the yield of methyldiphenylcyclohexanes fell to 6.6-7.2 g (26.4-28.8%). Increasing the amount of aluminum chloride to 18.6 g (0.14 mole) led to a decreased yield of both fractions (30 and 32%, respectively). Condensation in the presence of equimolar amounts of aluminum bromide gave 11.7 g (67.3%) of methylphenylcyclohexane and 4.1 g (16.4%) of methyldiphenylcyclohexanes.

Study of the methylphenylcyclohexanes. Judging by the refractive index ($n^{20}D$ 1.5348-1.5389), the first fraction contained a considerable amount of cycloolefins. It was freed from these by repeated washing with warm

sulfuric acid (d 1.75). After this treatment it was washed with water, dried, and distilled over sodium; the product had the constants:

B.p. 121-122° (18 mm), $n^{20}D$ 1.5295, d^{20}_4 0.9457, MR_D 56.84; calc. 56.43.

Found %: C 89.34; H 10.46. $C_{13}H_{18}$. Calculated %: C 89.59; H 10.41.

The benzamino derivative obtained from it in the usual way [5] was a mixture from which individual products could not be separated by fractional crystallization.

Dehydrogenation of the hydrocarbons with selenium in a sealed tube at 300-350° for 40 hr gave a product which distilled at 120-130° (20 mm) and partly crystallized. The greater part of the crystalline substance was diphenyl, with m.p. 69°; the lesser part was fluorene with m.p. 115°. Mixed melting points of these substances with known samples gave no depression of the melting points.

Study of the methyldiphenylcyclohexanes. The methyldiphenylcyclohexane fraction was obtained as a viscous, light yellow liquid which crystallized on standing. The liquid which remained after removal of the crystals was distilled over sodium.

B.p. 155-160° (2.5 mm), $n^{20}D$ 1.5715, d^{20}_4 1.0180, MR_D 80.86; calc. 80.54.

Found %: C 91.45; H 8.89. $C_{19}H_{22}$. Calculated %: C 91.14; H 8.86.

Fractional crystallization from alcohol of the solid portion and sorting of the crystals separated 1-methyl-2,5-diphenylcyclohexane, long, thin plates with m.p. 96-97°.

Found %: C 90.81; H 9.05. $C_{19}H_{22}$. Calculated %: C 91.14; H 8.86.

We also isolated some isomeric hydrocarbon in the form of prisms with m.p. 112-113°.

Found %: C 90.99, 91.07; H 8.85, 8.93. $C_{12}H_{22}$. Calculated %: C 91.14; H 8.86.

Heating 1 g of 1-methyl-2,5-diphenylcyclohexane with 0.2 g of platinized carbon (20% Pt) to weak boiling for 3-4 hr gave 1 methyl-2,5-diphenylbenzene which crystallized from alcohol in the form of tetragonal platelets or needles with m.p. 91-92°. The substance which solidified after melting sometimes melted again at 96-97°.

Found %: C 93.37, 93.47; H 6.57, 6.49. $C_{19}H_{16}$. Calculated %: C 93.40; H 6.60.

A sample mixed with 1-methyl-2,5-diphenylbenzene synthesized in another way gave no melting point depression and the mixture with the starting hydrocarbon melted below 80°.

Heating 1-methyl-2,5-diphenylbenzene with platinized carbon in a sealed tube at 350-400° for four hours gave 2-phenylfluorene which was purified by sublimation in a vacuum and crystallization from alcohol. M.p. 192-193°: a mixture with 2-phenylfluorene obtained by dehydrogenation of 2-cyclohexylfluorene [3] also melted at 192-193°.

2-Phenylfluorene mixed with 1-methyl-2,5-diphenylbenzene was obtained directly from 1-methyl-2,5-diphenylcyclohexane by long boiling of the latter with platinized carbon.

The methyldiphenylcyclohexane with m.p. 112-113° was entirely unchanged (partly sublimed) when boiled with platinized carbon or selenium. Reaction with the platinum catalyst occurred only at temperatures above 400° in a sealed tube. The catalyzate obtained after four hours heating was extracted with benzene and, after the latter had been distilled off, was distilled. From the distillate after long standing there separated crystals of the starting substance, m.p. 113°. The liquid residue was not studied.

The liquid portion of the methyldiphenylcyclohexanes was dehydrogenated in the presence of platinized carbon and selenium. When 4 g of the product was boiled with 0.5 g of platinized carbon, there was at first an intensive evolution of hydrogen, which gradually decreased. Heating was continued for about 25 hr. The catalyzate was extracted with benzene, and after distillation of the solvent was fractionated into two portions in a vacuum: the first boiling at 150-155° (3 mm) and the second at 175-185° (3 mm). The second fraction quickly crystallized; fractional crystallization from alcohol separated from it m-terphenyl, needles with m.p. 86°; 1-methyl-2,5-diphenylbenzene, tetragonal platelets with m.p. 92°; 2-phenylfluorene with m.p. 193-194°, and a substance with m.p. 84° which crystallized in the form of cubes. Heating 2.25 g of the fraction with 2 g of selenium for 8 hr gave a product which, after washing with alkali and drying, distilled at 200-215° (12 mm). On

standing, there precipitated from it crystals of p-terphenyl, which gave no depression of the melting point with commercial p-terphenyl.

Synthesis of 1-methyl-2,5-diphenylbenzene. 4-Cyclohexyl-o-cresol. A mixture of 91.8 g (0.85 mole) of o-cresol, 85.0 g (0.85 mole) of cyclohexanol, and 185 ml of phosphoric acid (d 1.86) was heated on a boiling water bath for 12 hr with stirring. The reaction product was separated from the phosphoric acid, washed with water, and then treated with excess 20% sodium hydroxide. The resulting phenolate of 4-cyclohexyl-o-cresol was filtered and washed, first with a solution of sodium hydroxide, and then several times with benzene. The precipitate was decomposed with dilute hydrochloric acid. The resulting 4-cyclohexyl-o-cresol was separated, washed with water, dried, and distilled. Yield 45.5 g (28.2%); b.p. 290-295° (720 mm). On standing, the product crystallized; recrystallization from ligroin gave a product with m.p. 77-78° which agreed with the literature [6].

2-Methyl-4-cyclohexylcyclohexanol (mixture of stereoisomers). Hydrogenation of 4-cyclohexyl-o-cresol was carried out with a rotating autoclave over Raney nickel in alcohol solution at 180-200° and 120 atm pressure of hydrogen at 20°. The reaction product after distillation of the alcohol was used without further purification for the following steps. Yield 93%. Very viscous, colorless liquid.

2-Methyl-4-cyclohexylcyclohexanone (mixture of stereoisomers). To 14.6 g of the mixture of 2-methyl-4-cyclohexylcyclohexanols dissolved in 50 ml of benzene and heated to 45-50° was added dropwise with stirring a solution of 7.7 g of sodium bichromate and 5 ml of concentrated sulfuric acid in 18 ml of water. The benzene solution was washed with water, dried, and fractionated. The ketone distilled at 155-158° (16 mm). Yield 12.9 g (89.6%), $n^{20}D$ 1.4881.

1-Phenyl-2-methyl-4-cyclohexylcyclohexanol (mixture of stereoisomers). This was obtained from 10.5 g of bromobenzene, 1.61 g of magnesium, and 12.9 g of 2-methyl-4-cyclohexylcyclohexanol in 50 ml of absolute ether. Since visible reaction did not occur when the ketone was added, the reaction mixture was boiled for several hours, at the end on a boiling water bath (after the ether had been distilled off); it was decomposed with dilute sulfuric acid. The alcohol was extracted with ether and after drying over potash and distillation of the ether was distilled. B.p. 167-170 (2-2.5 mm), $n^{20}D$ 1.5240. Thick, colorless liquid. Yield 7.0 g (38.7%).

1-Methyl-2,5-diphenylbenzene. When the alcohol was heated with 20% platinized carbon there was violent evolution of hydrogen and splitting out of water. The reaction ended after one hour. The product was extracted with benzene, the benzene solution was filtered, and after evaporation of the benzene the 1-methyl-2,5-diphenylbenzene was recrystallized from alcohol. Usually, the product crystallized in the form of thick quadratic plates, but sometimes it precipitated partly or wholly as long, thick needles. Both forms of crystals melted at 91-92° and on repeated melting of the solidified melt, at 96-97°. The substance gave no depression with the product obtained in the dehydrogenation of methyldiphenylcyclohexane with m.p. 96-97°, and a mixed melting point with this hydrocarbon melted below 80°.

Dehydrogenation of the alcohol under more severe conditions, first heating with platinized carbon as described above, and then in a sealed tube at about 400° for three hours, gave a product from which 2-phenylfluorene, m.p. 192-193°, was isolated by sublimation and then crystallization from alcohol.

SUMMARY

1. It has been shown that in the reaction of 1-phenyl-2-methylcyclohexanol with benzene in the presence of aluminum chloride or bromide there is formed a mixture of methylphenylcyclohexanes and a mixture of methyldiphenylcyclohexanes in which we have demonstrated the presence of 1-methyl-2,5-diphenyl-, 1-methyl-1,3-diphenyl-, and 1-methyl-1,4-diphenylcyclohexanes.

2. We have synthesized the undescribed 1-methyl-2,5-diphenylbenzene. 2-Phenylfluorene is obtained by its dehydrogenation.

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THE FORMATION OF DIALKYL ALUMINUM HALIDES FROM ALKYL ALUMINUM SESQUIHALIDES IN THE PRESENCE OF SODIUM HALIDES

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Translated from Zhurnal Obshchei Khimmi, Vol. 30, No. 6, pp. 1926-1929,
June, 1960
Original article submitted July 6, 1959

Recently, dialkyl aluminum halides have acquired great value in connection with their use as catalysts in the polymerization of α-olefins and ethylene [1] and as starting compounds for obtaining dialkyl aluminum hydrides [2, 3]. There is also great interest in the conversion of dialkyl aluminum halides under the influence of sodium fluoride into aluminum trialkyls [4]. Up to the present time, only one process has been known for getting dialkyl aluminum halides, namely, by the action of the calculated amount of aluminum halide or alkyl aluminum sesquihalide on trialkyl aluminums [5] according to the scheme:

$$2R_3Al + AlX_3 \longrightarrow 3R_2AlX,$$
$$R_3Al + R_3Al_2X_3 \longrightarrow 3R_2AlX. \quad X = Cl, Br.$$

This method is simple, but requires the use of aluminum trialkyls which themselves must be obtained by one or another method.

In the present work we have shown that a series of dialkyl aluminum halides R_2AlX(X = Cl, Br, I) can be obtained by symmetrization of alkyl aluminum sesquihalides with the corresponding sodium halide according to the scheme

$$2R_3Al_2X_3 + nNaX \longrightarrow 3R_2AlX + AlX_3 \cdot nNaX.$$

We studied this reaction with methyl and ethyl aluminum sesquichlorides, ethyl aluminum sesquibromide, and ethyl and propyl aluminum sesquiiodides. The method consisted in heating a mixture of the alkyl aluminum sesquihalide with the corresponding sodium salt at 200-220° and later distillation in a vacuum of the dialkyl aluminum halide. When the mixture of alkyl aluminum sesquihalide and sodium halide was heated, formation of two liquid layers occurred: the upper layer was dialkyl aluminum halide, the lower layer was a complex compound of alkyl aluminum dihalide and sodium halide which crystallized on cooling. This effect was found in all cases studied, that is, for chlorides, bromides, and iodides. Hall and Nash [6] showed earlier that on heating a mixture of sodium chloride with diethyl aluminum chloride and ethyl aluminum dichloride, the latter was bound in a complex which solidified on cooling. On distillation in a vacuum there occurred first distillation of the dialkyl aluminum halide from the upper layer, and then of dialkyaluminum halide formed by symmetrization of the complex of alkyl aluminum dihalide with the sodium salt. The yield of dialkyl aluminum halide calculated on the starting alkyl aluminum sesquihalide was 80-90%. In some cases it was expedient to repeat the heating of the dialkyl aluminum halide which was obtained with a small amount of sodium salt in order to get a purer product. After distillation of the dialkyl aluminum halide, there remained a solid residue from which aluminum halide could not be distilled off since it was evidently bound in a strong complex with the sodium salt.

Relation of Degree of Symmetrization of Ethyl Aluminum Sesquibromide to Ratio of Reagents

Mole ratio $(C_2H_5)_3Al_2Br_3$: NaBr	Bromine content in product, %
1 : 0.6	56.55
1 : 0.8	52.32
1 : 1	49.28
1 : 1.2	48.17
1 : 1	48.08

In the case of the ethyl aluminum sesquibromide we studied the effect of the amount of sodium bromide on the degree of symmetrization. We showed that with stirring of the reagents, full symmetrization occurred at a mole ratio of ethyl aluminum sesquibromide to sodium bromide of 1 : 1-1.2. With lower amounts of sodium bromide the distillation product was a mixture of diethyl aluminum bromide and ethyl aluminum dibromide with the predominance of the first depending on the ratio of reagents. If more sodium bromide than an equimolecular amount was used, in every case, there was formed diethyl aluminum bromide; deeper symmetrization did not occur (see Table). When the reaction was run without stirring, more sodium bromide was required for full symmetrization: the ratio of ethyl aluminum bromide to sodium bromide had to be 1 : 2 or better, 1 : 2.5.

On heating methyl aluminum sesquiiodide with sodium iodide and later distillation of the reaction product in a vacuum, there occurred symmetrization with formation of a mixture of dimethyl aluminum iodide and trimethyl aluminum. When the resulting mixture was distilled at atmospheric pressure over sodium iodide, full symmetrization to trimethyl aluminum occurred.

$$(CH_3)_3Al_2Br_3 + nNaI \rightarrow (CH_3)_3Al + AlBr_3 \cdot nNaI .$$

EXPERIMENTAL

I. Diethyl aluminum bromide. a) With stirring. We heated 52 g (0.14 mole) of ethyl aluminum sesquibromide (which contained 62.99% Br) with 17 g (0.17 mole) of ignited sodium bromide at 200-220° for two hours; formation of two liquid, immiscible layers occurred. After this was distilled, free ethyl aluminum bromide, b.p. 84-84.5° (3 mm) distilled off. When the rate of distillation slowed, the bath temperature was raised to 250-300°. The diethyl aluminum bromide which was formed by decomposition of the complex distilled at 85-100° (3 mm) because of the overheating of the reaction mixture; the distillation was accompanied by bumping and foaming. By repeated distillations we obtained 31 g (92%) of diethyl aluminum bromide with b.p. 84.2-85° (3 mm).

Found %: C 29.12, 29.36; H 6.14; 6.14; Al 16.54, 16.60; Br 48.30, 48.31. $C_4H_{10}AlBr$. Calculated %: C 29.10; H 6.05; Al 16.30; Br 48.42.

b) Without stirring. We heated 76.2 g (0.20 mole) of ethyl aluminum sesquibromide with 50 g (0.49 mole) of sodium bromide at 200° for 1.5 hr. Formation of two layers and a solid residue on the bottom of the flask took place. After cooling, the lower liquid layer solidified; the upper layer was poured off and by distillation gave 30 g of diethyl aluminum bromide. Distillation of the solid residue gave a further 12 g of diethyl aluminum bromide. Total yield 42 g (85%). Found: Br % 48.25, 48.37.

II. Dimethyl aluminum chloride. By heating 40 g (0.23 mole) of methyl aluminum sesquichloride with stirring with 15.8 g (0.27 mole) of sodium chloride there occurred strong boiling of the liquid. After distillation under conditions analogous to those of Expt. Ia, we obtained 26 g (84%) of dimethyl aluminum chloride with b.p. 85° (100 mm).

Found %: Cl 38.10, 38.18. C_2H_6AlCl. Calculated %: Cl 38.36.

III. Diethyl aluminum chloride. a) Analogously to Ia from 138 g (0.56 mole) of ethyl aluminum sesquichloride and 40 g (0.67 mole) of sodium chloride we obtained 85 g (85%) of diethyl aluminum chloride with b.p. 65-66° (2 mm).

Found %: C 39.34, 39.55; H 8.30, 8.37; Al 22.69, 22.45; Cl 29.09, 29.20. $C_4H_{10}AlCl$. Calculated %: C 39.85; H 8.36; Al 22.38; Cl 29.40.

b) Analogously to Expt. Ib from 343 g (1.39 mole) of ethyl aluminum sesquichloride and 200 g of sodium chloride without separating the mixture we obtained 195 g (79%) of diethyl aluminum chloride.

Found %: Cl 29.15, 29.40.

IV. Diethyl aluminum iodide. a) Analogously to Ia, from 53.3 g (0.102 mole) of ethyl aluminum sesquiiodide and 18.5 g (0.12 mole) of sodium iodide, we obtained 32 g (98%) of diethyl aluminum iodide with b.p. 91° (2 mm).

Found %: I 60.14, 60.03. $C_4H_{10}AlI$. Calculated %: I 59.85.

b) Analogously to Ib from 80 g (0.153 mole) of ethyl aluminum iodide and 57 g (0.381 mole) of sodium iodide we obtained 44 g (91%) of diethyl aluminum iodide.

Found %: I 59.60, 59.48.

V. Di-n-propyl aluminum iodide. We heated 59.2 g (0.128 mole) of n-propyl aluminum sesquiiodide with 48 g (0.320 mole) of sodium iodide. After distillation, accompanied by decomposition, we obtained a product with b.p. 156-165° (3 mm), which from the analytical data is dipropyl aluminum iodide with an admixture of propyl aluminum diiodide.

Found %: I 59.17, 59.08. $(n\text{-}C_3H_7)_2AlI$. Calculated %: I 52.95. $(n\text{-}C_3H_7)_3Al_2I_3$. Calculated %: I 67.51.

After repeated heating of this mixture with 15 g of sodium iodide we isolated by distillation 28 g (75%) of dipropyl aluminum iodide with b.p. 125-127° (1 mm).

Found %: I 52.81, 52.96.

VI. Trimethyl aluminum. We heated 84.2 g (0.17 mole) of methyl aluminum sesquiiodide to 180° with 65 g (0.43 mole) of sodium iodide. After distillation we obtained 32 g of substance with b.p. 62-80° (8 mm).

Found %: I 60.54, 60.86. $CH_3)_2AlI$. Calculated %: I 69.02.

This mixture was again heated with 22 g of sodium iodide with simultaneous distillation of the resulting trimethyl aluminum at such a rate that the temperature of the bath did not exceed 160-180°. We obtained 10 g (80%) of trimethyl aluminum with b.p. 125-126°.

SUMMARY

We have shown that alkyl aluminum sesquihalides $R_3Al_2X_3$ (X = Cl, Br, I) can be converted into dialkyl aluminum halides under the influence of the corresponding sodium halide.

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THE ALKYLATION OF 4-BROMOANISOLE BY PROPYLENE, PSEUDOBUTYLENE AND CYCLOHEXENE IN THE PRESENCE OF $BF_3 \cdot H_3PO_4$

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1929-1932, June, 1960
Original article submitted June 22, 1959

The alkyl ethers of haloalkylphenols are usually obtained by complex methods and therefore many of them have not been easily available up to now. In the development of our studies on alkylation of halogen substituted phenols by olefins in the presence of catalysts based on boron trifluoride, we report in the present paper on the results of an investigation of the reaction of 4-bromoanisole with propylene, pseudobutylene, and cyclohexene in the presence of the catalyst $BF_3 \cdot H_3PO_4$.

Our results permit us to consider that the reaction of alkylation of 4-bromoanisole by olefins is comparatively simple and suitable for preparing 2-alkyl-4-bromoanisoles. When 4-bromoanisole reacts with propylene and pseudobutylene in the presence of $BF_3 \cdot H_3PO_4$ at 30-70°, only monoalkyl-4-bromoanisoles are formed. At low temperatures (30°) alkylation of 4-bromoanisole goes best with pseudobutylene, and at 70° a higher yield of product is obtained in the reaction with propylene.

The best conditions, in which 2-isopropyl-4-bromoanisole and 2-sec-butyl-4-bromoanisole are obtained in yields of 64.5 and 58%, are molar ratios of 4-bromoanisole, olefin, and catalyst of 3 : 1 : 0.3, temperature 70° (for propylene) and 30° (for pseudobutylene), time of adding the olefin 2 hr (to 0.1 mole of bromoanisole), and further stirring of the reaction mixture at room temperature for two hr.

Cyclohexene shows considerable reactivity In distinction from propylene and pseudobutylene two products are obtained in this case: liquid 2-cyclohexyl-4-bromoanisole, and crystalline 2,6-dicyclohexyl-4-bromoanisole. Their total yield is 66-85%. The best conditions, in which 2-cyclohexyl-4-bromoanisole and 2,6-dicyclohexyl-4-bromoanisole are obtained in yields of 67 and 18%, are a mole ratio of 4-bromoanisole, cyclohexene, and $BF_3 \cdot H_3PO_4$ of 4 : 1 : 0.3, temperature 30°, duration of addition of cyclohexene to 0.1 mole of bromoanisole one hour, and further stirring the reaction mixture for two hours. The effect of the conditions on yield of alkylation products of 4-bromoanisole is shown in Tables 1 and 2. The composition and structure of the alkylation products was established by converting them into the known 3-alkyl-4-methoxybenzoic acids.

EXPERIMENTAL

4-Bromoanisole was obtained from p-anisidine by analogy with the synthesis of 4-bromotoluene [1].

B.p. 73° (2 mm), $n^{20}D$ 1.5616, d^{20}_4 1.4791, MR_D 40.92; calc. 40.33.

Propylene was obtained by dehydration of isopropyl alcohol; pseudobutylene, cyclohexene, and the catalyst were prepared as previously described [2].

TABLE 1

Alkylation of 4-Bromoanisole by Propylene and Pseudobutylene

Mole ratio of bromoanisole, propylene or pseudobutylene, and $BF_3 \cdot H_3PO_4$	Temp.	2-Alkyl-4-bromoanisole		
		yield, %	b.p. (pressure in mm)	n_D^{20}
Alkylation by propylene				
2 : 1 : 0.3	30°	30.1	90—94° (2)	1.5316
3 : 1 : 0.3	30	41.8	131—135 (22)	1.5360
3 : 1 : 0.3	50	51.2	80—87 (1)	1.5355
3 : 1 : 0.3	60	63.1	80—87 (1)	1.5350
3 : 1 : 0.3	70	64.5	79—86 (1)	1.5370
3 : 1 : 0.4	30	57.8	86—91 (2)	1.5325
3 : 1 : 0.4	60	62.8	81—87 (1)	1.5368
3 : 1 : 0.5	30	59.9	80—86 (1)	1.5330
4 : 1 : 0.3	30	22.5	80—85 (1)	1.5370
Alkylation by pseudobutylene				
1.5 : 1 : 0.15	30—35°	33.1	122 (5)	
2 : 1 : 0.2	30—35	36.6	140—142 (10)	
2 : 1 : 0.3	30	50.2	95—96 (3)	
3 : 1 : 0.2	30—35	44.3	113—116 (2)	
3 : 1 : 0.3	60	51.0	93—96 (3)	
3 : 1 : 0.3	30	57.9	98—99 (3)	
4 : 1 : 0.3	27—30	45.3	122—123 (5)	

TABLE 2

Alkylation of 4-Bromoanisole by Cyclohexene

Mole ratio of bromoanisole, cyclohexene, and $BF_3 \cdot H_3PO_4$	Temp.	Cycloalkylation products			
		2-cyclohexyl-4-bromoanisole			2,6-dicyclohexyl-4-bromoanisole (yield, %)
		Yield, %	B.p. (pressure in mm)	n_D^{20}	
2 : 1 : 0.3	30°	56.6	130—132 (2)	1.5562	26.5
3 : 1 : 0.1	30	49.2	142—146 (3)	1.5590	27.0
3 : 1 : 0.3	20	46.1	131—132 (2)	1.5590	20.4
3 : 1 : 0.3	30	57.9	126—132 (1)	1.5560	23.7
3 : 1 : 0.3	50	59.2	126—132 (1)	1.5540	22.2
3 : 1 : 0.3	60	59.8	128—132 (2)	1.5551	22.1
3 : 1 : 0.4	30	61.7	138—141 (3)	1.5558	20.2
4 : 1 : 0.3	30	67.0	130—132 (2)	1.5560	18.1

Alkylation of 4-bromoanisole by propylene. In a three-necked flask fitted with mechanical stirrer, thermometer, and bubbler, was placed a weighed amount of anhydrous orthophosphoric acid and it was saturated with boron trifluoride to a weight corresponding to 8-30% excess over the formula $BF_3 \cdot H_3PO_4$. Then 4-bromoanisole was added and the mixture, a homogeneous liquid, was heated to a given temperature. Then propylene was introduced in the quantity of 0.1 mole. As the propylene was introduced, the reaction mixture first became yellowish, and at the end of the experiment became a clear, dark brown liquid. After the propylene had been added, the reaction mass was stirred for two hours more at room temperature, and allowed to stand for 12-16 hr, then it was dissolved in benzene, washed with water, with 5% soda, with water again, and was dried with calcium chloride. After washing with water the mixture changed from dark brown to yellowish, and after neutralization with soda solution, it became a colorless liquid. The benzene was distilled off at atmospheric pressure and

the residue was distilled in a vacuum. After separation of unreacted 4-bromoanisole, the alkylation product, which was 2-isopropyl-4-bromoanisole, boiled off within a range of 1-7°. In the distillation flask there remained 1-2 g of dark brown tar which quickly hardened in air.

2-Isopropyl-4-bromoanisole (I) after repeated distillations was a colorless, easily mobile liquid with a weak anisole odor.

B.p. 86-87° (2 mm), d^{20}_4 1.2462, $n^{20}D$ 1.5360, MR_D 57.18; calc. 54.17.

Found %: Br 35.11. $C_{10}H_{13}OBr$. Calculated %: Br 34.88.

3-Isopropyl-4-methoxybenzoic acid. In a flask fitted with a stirrer, reflux condenser, and dropping funnel was placed 2.44 g of magnesium in 40 ml of absolute ether. Slowly, with constant stirring, a mixture of 5.45 g of ethyl bromide and 11.45 g of (I) in 20 ml of absolute ether was added from the dropping funnel. Then the mixture was stirred for 30 min with heating to weak boiling, the flask was cooled with ice, and the reaction mass was treated with solid carbon dioxide until the flask was covered with ice on the outside, then hydrochloric acid was added to an acid reaction to Congo, the acidified solution was extracted with ether, the ether layer was separated and shaken with a 10% soda solution which was again acidified with hydrochloric acid and the acid which precipitated was filtered off. Yield 8.15 g (84%). Glittering white crystals. M.p. 163.5-164°(from aqueous methanol). According to the literature, m.p. 164-164.5°.

Alkylation of 4-bromoanisole with pseudobutylene. The reaction was carried out in the same way as with propylene. The single alkylation product was 2-sec-butyl-4-bromoanisole, which on distillation distilled within a range of 1-2°.

2-sec-Butyl–4-bromoanisole (II) after repeated distillations was a colorless oil with a weak anisole odor.

B.p. 110-111° (5 mm) d^{20}_4 1.2450, $n^{20}D$ 1.5364, MR_D 60.87; calc. 59.12.

Found %: Br 33.00, 33.20. $C_{11}H_{15}OBr$. Calculated %: Br 32.87.

3-sec-Butyl-4-methoxybenzoic acid was obtained from (II) by the method described for 3-isopropyl-4-methoxybenzoic acid, with a yield of 81.4%. Glittering white crystals. M.p. 165° (from aqueous methanol).

Alkylation of 4-bromoanisole with cyclohexene. The reaction was carried out as described above for propylene. After the corresponding treatment of the reaction mass, the alkylate was dried and vacuum distilled from a Favorskii flask. The monocyclohexylbromoanisole usually distilled as a narrow fraction, boiling in a range of 1-4°; the dicyclohexylbromoanisole remained in the distillation flask and quickly crystallized at room temperature. The position of the cylcohexyl radical was shown by transformation of the alkylation product into 3-cyclohexyl-4-methoxybenzoic acid.

2-Cyclohexyl-4-bromoanisole (III) after repeated distillations was a colorless, viscous liquid, almost without odor.

B.p. 132-133° (2 mm), d^{20}_4 1.2749, $n^{20}D$ 1.5602, MR_D 68.32; calc. 65.83.

When (III) stood for about three months, it crystallized into a snow white mass. M.p. 44.5-45° (from anhydrous alcohol).

Found %: Br 29.86, 29.80. $C_{13}H_{17}OBr$. Calculated%: Br 29.69.

3-Cyclohexyl-4-methoxybenzoic acid, obtained by the method for (I) and (II), appeared as glittering white plates. M.p. 192.5-193° (from methanol). Literature data [4]: m.p. 194-195°.

2,6-Dicyclohexyl-4-bromoanisole (IV)—a white crystalline compound. M.p. 160-161° (from ether).

Found%: Br 22.87, 22.58. $C_{19}H_{27}OBr$. Calculated %: Br 22.75.

SUMMARY

We have studied the alkylation of 4-bromoanisole by propylene, pseudobutylene, and cyclohexene in the presence of $BF_3 \cdot H_3PO_4$ at various mole ratios of reagents, amounts of catalysts, and temperatures. It was shown that in the reaction with propylene and pseudobutylene, monoalkylbromoanisoles were formed, and in the reaction

with cyclohexene, mono- and dicyclohexylbromoanisoles. The methoxy group is the strongest orienting influence, since all the mono derivatives were 2-alkyl-4-bromoanisoles. The yields of 2-isopropyl-4-bromoanisole, 2-sec-butyl-4-bromoanisole, and 2-cyclohexyl-4-bromoanisole were 64.5, 57.9, and 67%, respectively.

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THE HYDROGENOLYSIS OF TETRAHYDROFURANS

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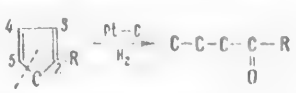
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1933-1937, June, 1960
Original article submitted June 29, 1959

The problem of the reaction mechanism of hydrogenolysis in the furan ring including in particular the question of the possibility of intermediate formation of a tetrahydrofuran in this reaction poses an experimental problem of the comparative investigation of the behavior of furans and the tetrahydrofuran compounds which correspond to them under ordinary conditions of hydrogenation. The studies carried out in this direction have led to the following results: under those conditions in which there occurs hydrogenolysis of the furan ring, the tetrahydrofuran ring either remains unchanged, or undergoes splitting in some other way than does the furan ring. In the hydrogenation of furan and tetrahydrofuran [1], or of furyl and tetrahydrofuryl alcohols [2] in the liquid phase over Adams platinum catalysts, only furan and furyl alcohol undergo hydrogenolysis, while their hydrogenated derivatives remain without change. On copper chromite, also in the liquid phase, furyl alcohol is split in almost equal degree at the 1,2 C-O bond and at the 1,5 bond, as a result of which there are formed the corresponding 1,5-pentanediol and the 1,2-pentanediol. Under the same conditions, tetrahydrofuryl alcohol undergoes hydrogenolysis to a very slight extent and in only one direction, at the 1,2 C-O bond with formation of the 1,5-pentanediol [3]. Wilson [4] studied the comparative hydrogenolysis of sylvane and tetrahydrosylvane in the vapor phase over a nickel catalyst and found that at 100° tetrahydrosylvane remained without change, and at 250° it formed a considerable quantity of gaseous products and did not at all form methylpropyl ketone, the chief product of the hydrogenolysis of sylvane.

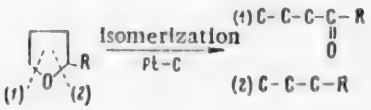
Since all these investigations were carried out in order to explain the mechanism of hydrogenolysis of the furan ring, they have established sufficiently only the differing relation of the furan and tetrahydrofuran rings to the hydrogenolysis reaction and have not entered into details with respect to the possible transformation of tetrahydrofurans under conditions of catalytic hydrogenolysis. However, it is perfectly clear that the study of the hydrogenolysis reaction of tetrahydrofurans, aside from the need to have information on the mechanism of hydrogenolysis of the furan ring, also has the importance that it emphasizes more definitely the specific difference between the furan and tetrahydrofuran rings in their relation to the hydrogenolysis reaction. In particular, the results of the study of hydrogenolysis of tetrahydrofurans in the present work leads to this conclusion.

1. As is known [5] α-alkylfurans undergo smooth hydrogenolysis under conditions of hydrogenation on platinized carbon in the vapor phase at 275° and normal pressure. The furan ring is then split exclusively at the 1,5 C-O bond which is not next to the alkyl radical side chain.

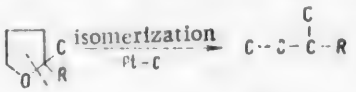


Hydrogenolysis of the furan ring does not occur through a stage of formation of a dihydrofuran, nor through a stage of formation of tetrahydrofurans [6]. As we have recently shown [7], the latter can be isomerized over platinized carbon in the vapor phase to carbonyl compounds with an open chain; however, this reaction occurs much more slowly than the hydrogenolysis of the furan ring, and in two directions, with formation of a ketone

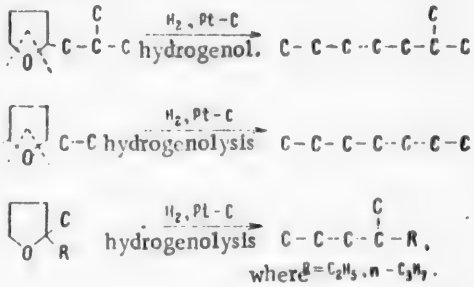
and an aliphatic hydrocarbon, the product of the removal of the carbonyl group of the aldehyde which is formed as an intermediate.



Isomerization of the ring of 2,2-dialkyltetrahydrofurans occurs exclusively at the C-O bond which is next to the side chain, and this leads only to the formation of aliphatic hydrocarbons.

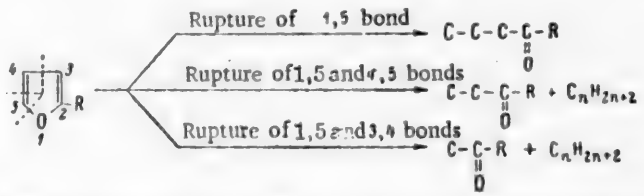


The reaction of isomerization of tetrahydrofurans is the only reaction which occurs when the vapors of these compounds are carried over platinized carbon in the absence of hydrogen. If hydrogen is passed along with the tetrahydrofuran vapors in the reaction system, then besides the isomerization of the tetrahydrofuran ring, there occurs its hydrogenolysis, and (in distinction from hydrogenolysis of the furan ring) this occurs on both C-O bonds with formation of aliphatic hydrocarbons.

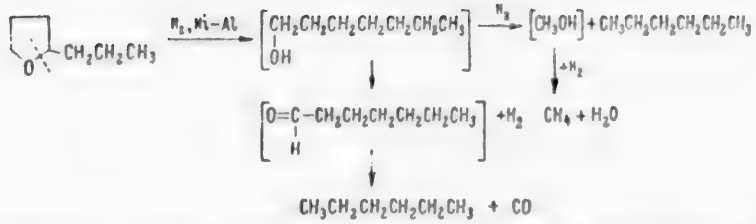


For all the homologs of tetrahydrofuran there is found formation of about the same amounts of products of isomerization and hydrogenolysis: 50-60% of isomerization products and 40-50% of hydrogenolysis products.

2. On a skeletal nickel-aluminum catalyst in the vapor phase at normal pressure there occurs the unusual, so-called "conjugated" hydrogenolysis of the furan ring [8]. Here, from the molecule of α-alkylfuran there are formed a molecule of aliphatic hydrocarbon and a molecule of aliphatic alcohol or ketone. This suggests rupture of not only the C-O bond, but also the C-C bond in the furan ring.



Hydrogenolysis of the furan ring on a skeletal nickel-aluminum catalyst becomes apparent even at 120-150°. At this temperature, the tetrahydrofuran ring is stable and practically does not undergo hydrogenolysis. At a higher temperature (275°) there is splitting of the tetrahydrofuran ring accompanied by formation of water and a considerable quantity of gaseous products. Analysis of the liquid part of the catalyzate shows that on a skeletal nickel-aluminum catalyst hydrogenolysis of a tetrahydrofuran ring with 1 or 2 radicals in the α-position occurs quite differently from the hydrogenolysis of the furan ring. Thus, for example, from 2-n-propyltetrahydrofuran and 2-methyl-2-ethyltetrahydrofuran we obtained respectively, n-hexane and 3-methylpentane, which shows that the tetrahydrofuran ring in these compounds undergoes hydrogenolysis at the C-O bond next to the side alkyl groups. The formation of aliphatic hydrocarbons which have one less carbon atom in the chain than the molecule of the original tetrahydrofuran is possible as a result of the following reactions:



Considering the hydrogenolysis reactions of homologs of furan and tetrahydrofuran from the point of view of the value of the resulting products, we should note that the hydrogenolysis of furans has a certain advantage, since it leads to the formation of aliphatic alcohols and ketones which are difficult to prepare and are useful in various syntheses, while the hydrogenolysis of tetrahydrofurans gives less valuable paraffin hydrocarbons. The reaction of hydrogenolysis of the tetrahydrofuran ring can be of some value for the synthesis of branched paraffin hydrocarbons from α-substituted tetrahydrofurans.

EXPERIMENTAL

Starting substances. 2-n-Propyltetrahydrofuran, 2-isobutyltetrahydrofuran, and 2-methyl-5-ethyltetrahydrofuran were obtained by hydrogenation of the corresponding homologs of furan in the vapor phase over platinized carbon at 150-170°. 2-Methyl-2-ethyltetrahydrofuran and 2-methyl-2-n-propyltetrahydrofuran were synthesized from 2-methyl-4,5-dihydrofuran by the method of Paul [9]. The tetrahydrofurans which were obtained had the properties shown in Table 1.

TABLE 1

Properties of Tetrahydrofuran Homologs

Name	B.p. at 750 mm	d_4^{20}	n_D^{20}
2-n-Propyltetrahydrofuran . . .	131.5—132.5°	0.8362	1.4232
2-Isobutyltetrahydrofuran . . .	149—150	0.8484	1.4285
2-Methyl-5-ethyltetrahydrofuran . . .	116.5—117	0.8403	1.4130
2-Methyl-2-ethyltetrahydrofuran . . .	120—121	0.8561	1.4194
2-Methyl-2-n-propyltetrahydrofuran . .	143.5—144	0.8528	1.4247

TABLE 2

Properties of Hydrogenolysis Products from Tetrahydrofuran Homologs

Tetrahydrofuran homologs	Catalyst	Temp.	Hydrogenolysis product	Yield, %	B.p.	d_4^{20}	n_D^{20}
2-Isobutyltetrahydrofuran	Pt—C	350°	2-Methylheptane	45	116—118°	0.6987	1.3947
2-Methyl-5-ethyltetrahydrofuran	Pt—C	350	n-Heptane	49	97—99	0.6847	1.3870
2-Methyl-2-ethyltetrahydrofuran	Pt—C	350	3-Methylhexane	~50	91—92.5	0.6865	1.3888
2-Methyl-2-n-propyltetrahydrofuran	Pt—C	350	4-Methylheptane	45	117—118	0.7161	1.3982
2-n-Propyltetrahydrofuran	Ni—Al	275	n-Hexane	~40	68—69.5	0.6600	1.3746
2-Methyl-2-ethyltetrahydrofuran	Ni—Al	275	3-Methylpentane	~40	63—64	0.6640	1.3763

Catalysts. The preparation of the catalysts, platinum on carbon and skeletal nickel-aluminum, was described previously [5, 8].

Conditions for Carrying Out the Reaction and Analysis of the Resulting Products

The reaction of hydrogenolysis of tetrahydrofurans was carried out in the vapor phase at normal pressure, that is, under those conditions at which we previously studied the hydrogenolysis of furan homologs. Hydrogenolysis on platinum was carried out at 350°, and on skeletal nickel-aluminum catalyst, at 275°. The starting substance was supplied over the catalyst at a volume rate of 0.1 hr^{-1}. The resulting catalyzate, after being dried with calcium chloride, was fractionated on an effective column. The substances isolated in pure form, carbohydrates and ketones, were identified by determining their physical constants. Semicarbazones were obtained from the ketones. In Table 2 we give the properties of the hydrogenolysis products from tetrahydrofuran homologs over platinized carbon and skeletal nickel-aluminum catalysts.

SUMMARY

1. We have studied the hydrogenolysis of 2-alkyl-, 2,2-dialkyl-, and 2,5-dialkyltetrahydrofurans in the vapor phase at normal pressure over platinized carbon and skeletal nickel-aluminum catalysts.

2. Hydrogenolysis of tetrahydrofuran homologs requires a higher temperature and goes in an entirely different manner than the hydrogenolysis of furan compounds.

3. On platinized carbon at 350° tetrahydrofurans besides being isomerized into aliphatic carbonyl compounds undergo hydrogenolysis at the same time at both C-O bonds, as a result of which there is formed a paraffin hydrocarbon with the same number of carbon atoms as the molecule of starting tetrahydrofurans.

4. On a skeletal nickel-aluminum catalyst, 2-alkyl and 2,2-dialkyltetrahydrofurans undergo hydrogenolysis at the C-O bond next to the side alkyl groups. Here the intermediately formed primary alcohol or aldehyde undergoes reactions leading to formation of paraffin hydrocarbons whose carbon chain contains one less carbon atom than the molecule of starting tetrahydrofuran. On a skeletal nickel-aluminum catalyst there is also a deeper splitting of the tetrahydrofurans with formation of water and gaseous products.

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THE REACTION OF NITROOLEFINS WITH ACYL HALIDES

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1937-1941,
June, 1960
Original article submitted February 23, 1959

Primary nitrocompounds under the action of dry hydrogen chloride, thionyl chloride, or acyl chlorides are converted into the corresponding hydroxamic acid chlorides or their acylated derivatives [1]. This reaction is general for primary nitroparaffins, and does not occur with secondary nitroalkanes. The relation of nitroolefins to these reagents has not been sufficiently studied [2]. More detailed study of this reaction showed [3] that nitroolefins react with anhydrous hydrogen chloride in ether solution with formation of 1,2-dichloronitrosocompounds, which in the presence of an α-hydrogen atom rearrange into α-chlorohydroxamic acid chlorides.

The hydrolysis products of the latter are hydroxylamine hydrochlorides [2]. An analogous nitrosooxime rearrangement occurs with α-nitroolefins in the reaction with aromatic hydrocarbons under the conditions of the Gustavson-Friedel-Crafts reaction.

β-Nitroolefins here give the normal addition product [4]. A study of the action of nitrosyl chloride on halogenated ethylenes showed [5] that if the carbon atom is bound to halogen and nitroso groups at the same time, a rearrangement occurs, as a result of which hydroxamic acid halides are obtained.

The present work is concerned with the investigation of the reaction of α-nitroolefins with acyl halides. We would here expect the formation either of halogen nitroketones as the normal product, or hydroxamic acid halides. It was shown that all the α-nitroolefins studied undergo, under the action of acyl halides, a nitroso-oxime rearrangement with the formation of α-halogen-N-acylhydroxamic acid halides and the separation of the corresponding organic acid according to the general scheme

$$RCH=C(CH_3)NO_2 + 2R'COX \rightarrow RCHX-C(=NOCOR')X + R'COOH,$$

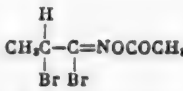
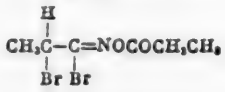
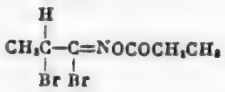
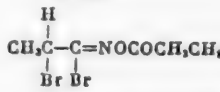
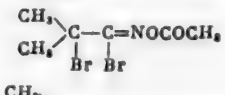
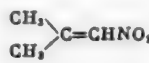
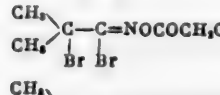
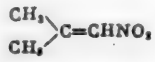
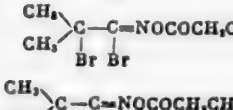
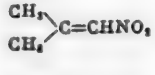
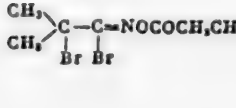
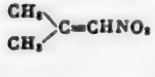
The reaction occurs easily with evolution of heat and is hastened by the presence of acid catalysts $ZnCl_2$, $ZnBr_2$, and H_2SO_4. The end products are obtained in good yield. The formation of intermediate nitrosocompound is indicated by the blue-green color of the reaction mixture, which disappears at the end of the reaction.

It is suggested that the primary addition goes in the 1,4 position [3] of $(CH_3)_2C=CHNO_2$, and then to the C = N bond with splitting of acid

The structure of the α-halogen-N-acylhydroxamic acids was confirmed by hydrolyzing α-bromo-N-propionylhydroxamic acid bromide, as a result of which we isolated hydroxylamine hydrobromide, α-hydroxy-isobutyric, propionic, and hydrobromic acids.

All the α-bromo-N-acylhydroxamic acid halides which we synthesized gave a red color with an aqueous alcoholic solution of ferric chloride. Products of this type can serve as intermediates for further synthesis [6].

Tertiary nitroolefins under analogous conditions react with only one molecule of halide, but the product of the reaction could not be separated in analytically pure form, since it evidently distilled with the starting

No.	Catalyst	Formula	Starting nitroolefin	B.p. (pressure in mm)	n_D^{20}	d_4^{20}	Yield, %	Calc. %		Found. %	
								C	H	C	H
1	$ZnCl_2$		$CH_3CH{=}CHNO_2$	89—90° (2)	1.5278	1.8385	62.3	21.98	2.56	21.72, 21.85	2.69, 2.60
2	$ZnCl_2$		$CH_3CH{=}CHNO_2$	97—98 (1)	1.5210	1.7302	50.0	25.09	3.14	25.07, 25.20	3.08, 2.99
3	—		$CH_3CH{=}CHNO_2$	100 (1)	1.5232	1.7370	60.0	25.09	3.14	24.83, 24.92	3.16, 3.13
4	—		$CH_3CH{=}CHNO_2$	105—107 (1)	1.5152	1.6349	34.0	27.91	3.65	28.01, 28.10	3.74, 3.79
5	$ZnCl_2$			117—119 (12)	m.p.	28—28.5°	32.0	25.09	3.14	25.16, 25.21	3.11, 3.02
6	$ZnCl_2$			87—88 (1)	1.5150	1.6111	72.3	27.91	3.65	28.20, 28.40	3.85, 3.81
7	—			99—100 (2)	1.5100	1.6148	60	27.94	3.65	28.12, 28.31	3.80, 3.84
8	$ZnCl_2$			112—113 (3)	1.5108	1.5698	57	30.50	4.12	30.61, 30.68	4.26, 4.19

nitroolefin. It was noted that the addition of acid bromide to the tertiary nitroolefin was accompanied by evolution of a large amount of heat (even without using a catalyst).

In the table we give the physical properties and yields of the compounds which we synthesized.

EXPERIMENTAL

The nitroolefins were prepared by the method of dehydration of the corresponding nitroalcohols with phthalic anhydride [7]; the alcohols were obtained by aldehyde-nitroparaffin condensation [8].

1. Action of propionyl bromide on 1-nitro-1-propene. a) In a three-necked flask, capacity 100 ml, fitted with a reflux condenser was placed 13.6 g of 1-nitro-1-propene and 41.8 g of propionyl bromide. The reaction mixture at once became green-blue. After one hour the temperature had risen from 16° to 70°; the liquid gradually took on a pale yellow color and the temperature fell. The mixture was heated to 80° on a water bath, cooled, and distilled in a vacuum.

The first fraction was propionic acid; the second fraction, which was distilled at 1 mm, was α-bromo-N-propionylpropionohydroxamic acid bromide, a mobile, colorless liquid which grew slightly turbid on standing and had an obtrusive unpleasant odor. Yield 27.0 g (60%).

B.p. 100° (1 mm), d^{20}_4 1.7370, $n^{20}D$ 1.5232.

Found %: C 24.83, 24.92; H 3.16, 3.13. $C_6H_9O_2NBr_2$. Calculated %: C 25.09; H 3.14.

b) In a three-necked round bottom flask cooled to −16° was placed 31.1 g of 1-nitro-1-propene, 0.25 g of anhydrous $ZnCl_2$, and 98 g of propionyl bromide was gradually added. The solution acquired a green-blue color; the temperature rose. Then the mixture was heated to 70° and after cooling was distilled in a vacuum.

First fraction, propionic acid, 26.5 g (theoretical amount); second fraction, the acid bromide. Yield 50 g (50%).

B.p. 97-98° (1 mm), d^{20}_4 1.7302, $n^{20}D$ 1.5210.

Found %: C 25.07, 25.20; H 3.08, 2.99. $C_6H_9O_2NBr_2$. Calculated %: C 25.09; H 3.14.

2. Action of propionyl bromide on 1-nitro-2-methyl-1-propene. To 16 g of nitromethylpropene was added 43.4 g of propionyl bromide. The solution became green. The temperature rose to 40°. The mixture was further heated to 80° and after cooling was vacuum distilled; we isolated propionic acid and α-bromo-N-propionyl-α-methylpropionohydroxamyl bromide, 28 g (60%).

B.p. 99-100° (3 mm), d^{20}_4 1.6148, $n^{20}D$ 1.5100.

Found %: C 28.12, 28.31; H 3.80, 3.84. $C_7H_{11}O_2NBr_2$. Calculated %: C 27.91; H 3.65.

In a round bottom flask with a reflux condenser we placed 9.5 g of α-bromo-N-propionyl-α-methylpropionohydroxamyl bromide and 95 ml of water. The mixture was boiled for three hours at a bath temperature of 120°. After the solution had cooled we obtained from the homogeneous mixture by mild vacuum distillation a distillate in which titration by sodium hydroxide determined the content of propionic and hydrobromic acids. In the neutralization we used 110 ml of 0.5 N NaOH which corresponded to a total content of 4.01 g of acid. Titration with 1% $AgNO_3$ established the presence of 1.83 g of HBr in the distillate. The solid residue which remained in the flask after distillation of the aqueous solution of acids was treated with ether, from which we isolated 2.1 g of α-hydroxybutyric acid with m.p. 78-79° (from benzene) and from the portion of the residue insoluble in ether we obtained 3 g of hydroxylamine hydrobromide.

3. Action of butyryl bromide on 1-nitro-2-methyl-1-propene. In the reaction we took 17.3 g of nitroisobutene, 52 g of butyryl bromide, and 0.25 g of anhydrous $ZnCl_2$. The yield of α-bromo-N-butyryl-α-methylpropionohydroxamyl bromide was 30.7 g (57%).

B.p. 112-113° (3 mm), d^{20}_4 1.5698, $n^{20}D$ 1.5108.

Found %: C 30.61, 30.68; H 4.26, 4.19. $C_8H_{13}O_2NBr_2$. Calculated %: C 30.50; H 4.12.

The other acid bromides of α-bromo-N-acylhydroxamic acids were obtained in an analogous way.

SUMMARY

It is shown that α-nitroolefins react with acyl bromides to give a nitrosooxime rearrangement, as a result of which α-bromo-N-acylhydroxamyl bromides are formed. The acid bromides which were synthesized have not been described.

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PHENYLAMIDES OF N-DIANILIDOPHOSPHINYL ARYLIMINOSULFONIC ACIDS

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1941-1946,
June, 1960
Original article submitted May 7, 1959

The phenylamides of N-dianilidophosphinyl aryliminosulfonic acids are derivatives of the unknown amides of iminosulfonic acids RSO (= NH)NH_2. Until now, only two derivatives of iminosulfonic acid amide have been known: p-carboxyphenylsulfonylamide of N-p-carboxyphenylsulfonyl ethane- and benzenesulfonic acids, RSO(= $NSO_2C_6H_4COOH$-p)$NHSO_2C_6H_4COOH$-p (R = C_2H_5 and C_6H_5), obtained by permanganate oxidation of p-methylphenylsulfonylamide of N-p-methylphenylsulfonylethane- and benzene iminosulfonic acids, RS(= $NSO_2C_6H_4CH_3$-p)$NHSO_2C_6H_4CH_3$-p (R = C_2H_5 and C_6H_5) [1]. The properties of these compounds were not studied, and the authors themselves did not consider their structures proved.

The recently obtained [2] acid chlorides of N-dichlorophosphinylaryliminosulfonic acids can be considered as starting substances for the synthesis of various N-substituted amides of the aryliminosulfonic acid type ArSO-[=NPO$(NXY)_2$]NXY. When aniline acts on the acid chlorides of N-dichlorophosphinyl aryliminosulfonic acids good yields are obtained of the phenylamides of N-dianilidophosphinyl aryliminosulfonic acids (Table 1).

$$ArSO(=NPOCl_2)Cl \xrightarrow{+6C_6H_5NH_2} ArSO[=NPO(NHC_6H_5)_2]NHC_6H_5.$$

The phenylamides of N-dianilidophosphinyl aryliminosulfonic acids are colorless, comparatively high melting, crystalline compounds, not soluble in the usual organic solvents, with the characteristics of rather strong acids, resembling in chemical properties the arylamides of arylsulfonic acids and the dianilides of arylsulfonamidophosphoric acids [3]. Their acid character probably depends on tautomerism with the corresponding dianilidophosphinylamides of N-phenyl aryliminosulfonic acids.

$$ArSO[=NPO(NHC_6H_5)_2]NHC_6H_5 \rightleftarrows ArSO(=NC_6H_5)NHPO(NHC_6H_5)_2.$$

When the phenylamides are heated they dissolve not only in sodium hydroxide solutions, but also in soda solutions. The acids are precipitated unchanged from alkali solution. When heated with concentrated sulfuric or hydrochloric acids they are hydrolyzed; they slowly precipitate from solution and are difficult to crystallize, which is probably explained by the existence of several tautomeric forms of racemic compounds which easily pass into each other. Apparently the most difficultly soluble forms of the tautomeric racemates precipitate from the solution. Theoretically, each phenylamide should exist in at least two racemic tautomers, and the possibility is not excluded that each of the tautomers can exist in the form of two racemates, cis and trans on the S = N bond.

The phenylamides of N-dianilidophosphinyl aryliminosulfonic acids are isomers of trianilidophosphazosulfonaryls [3], but differ sharply from them in physical and chemical properties and give melting point depressions with them; they are stronger acids than the trianilidophosphazosulfonaryls; they are markedly more easily soluble in the majority of organic solvents and melt much lower than the trianilidophosphazosulfonaryls, except for the phenylamide of N-dianilidophosphinyl-o-chlorobenzeneiminosulfonic acid.

TABLE 1

Phenylamides of N-Dianilidophosphinyl Aryliminosulfonic Acids of the Type $XC_6H_4SO[=NPO(NHC_6H_5)_2]NHC_6H_5$

X	Yield, %	M.p.	External form	Composition of molecule	% N		Solubility*				
					found	calc.	alcohol	benzene	ether	acetone	CCl_4
H	68	174—176°	Needles	$C_{24}H_{23}O_2N_4SP$	12.24, 12.40 *M* 446 **	12.12 *M* 462	+	+	=	+	=
o-CH_3	95	166—167	Prisms	$C_{25}H_{25}O_2N_4SP$	12.06, 12.11	11.76	+	+	=	+	=
p-CH_3	85	214—215	Needles	$C_{25}H_{25}O_2N_4SP$	11.61, 11.46	11.76	−	+	=	+	=
p-CH_3O	89	161—162	Prisms***	$C_{25}H_{25}O_3N_4SP$	11.57, 11.54	11.38	+	+	−	+	−
o-Cl	76	237—238	Prisms	$C_{24}H_{22}O_2N_4SPCl$	10.85, 10.87	11.27	+	+	=	+	=
p-Cl	95	190—192	Quadratic plates	$C_{24}H_{22}O_2N_4SPCl$	11.16, 10.95	11.27	+	−	=	+	−
p-Br	95	192—193	Prisms	$C_{24}H_{22}O_2N_4SPBr$	10.30, 10.20	10.35	+	−	=	−	−
p-F	88	154—155	Prisms	$C_{24}H_{22}O_2N_4SPF$	11.78, 11.95	11.66	+	−	=	+	−
m-CF_3	32	182—183	Needles	$C_{25}H_{22}O_2N_4SPF_3$	10.76, 10.68	10.56	+	+	−	+	−

* ++ Easily soluble at 20°; + little soluble at 20°, easily soluble at the boiling point; − little soluble at the boiling point; = insoluble at the boiling point.

** Rast method.

*** Gives a crystalline hydrate. Dried in vacuum before analysis .

TABLE 2

Trichlorophosphazosulfonaryls of the Type $XC_6H_4SO_2N = PCl_3$

X	M.p.	External form, solvent of crystallization	Composition of molecule	Found		Calc. % Cl**	Solubility ***	
				% Cl	equiv.*		ether	benzene
p-CH_3O	83—84°	Plates, CCl_4	$C_7H_7O_3NSPCl_3$	32.74, 32.73	4.97, 4.99	32.98	+	+
p-Br	82—83	Prisms, ligroin	$C_6H_4O_2NSPCl_3Br$	28.27, 28.41	4.89, 4.88	28.69	+	+
o-Cl	83—84	Prisms, CCl_4	$C_6H_4O_2NSPCl_4$	43.05, 43.12	4.98, 4.95	43.36	+	+

*Equivalents after hydrolysis.

**For all compounds the calculated equivalent after hydrolysis was 5.00.

***Signs as in Table 1. All the substances were difficultly soluble in boiling ligroin, and easily soluble in boiling carbon tetrachloride.

TABLE 3

Acid Dichlorides of Arylsulfonamidophosphoric Acids of the Type $XC_6H_4SO_2NHPOCl_2$

X	Yield %	M.p.	External form	Composition of molecule	Found		Calc.**** % Cl
					% Cl	equiv.	
p-CH_3O	93	128—129°	Needles	$C_7H_8O_4NSPCl_2$	23.34, 23.20	3.97, 4.01	23.22
p-Br	97	157—158	Prisms	$C_6H_5O_3NSPCl_2Br$	19.85, 19.71	3.94, 3.91	20.08
o-Cl	81	156—157	Prisms	$C_6H_5O_3NSPCl_3$	34.50, 34.56	3.99, 3.97	34.49

****For all the compounds the calculated equivalent after hydrolysis was 4.00.

For the synthesis of the phenylamides of N-dianilidophosphinyl aryliminosulfonic acids and for comparison of their properties with the isomeric trianilidophosphazosulfonaryls we prepared the undescribed trichlorophosphazosulfonaryls (Table 2), acid dichlorides of arylsulfonamidophosphoric acids (Table 3), triaryloxyphosphazosulfonaryls (Table 4), and trianilidophosphazosulfonaryls (Table 5) by the methods previously described [4].

EXPERIMENTAL

Phenylamides of N-dianilidophosphinyl aryliminosulfonic acids (Table 1). To a solution of 0.01 mole of acid chloride of N-dichlorophosphinyl aryliminosulfonic acids in 25 ml of benzene was slowly added a solution of 0.08 mole of aniline in 25 ml of benzene and the mixture was boiled on a water bath for 1-2 hr. After cooling, the precipitate of aniline hydrochloride was filtered off and the benzene was distilled off in a vacuum. The residue was washed with dilute hydrochloric acid and water; the reaction product then solidified and was filtered and recrystallized from alcohol, except for the phenylamide of N-dianilidophosphinyl p-tolueneiminosulfonic acid, which was recrystallized from aqueous dioxane. The phenylamides of N-dianilidophosphinyl p-bromo- and p-fluorobenzeneiminosulfonic acids were difficultly soluble in benzene and therefore precipitated

TABLE 4

Triaryloxyphosphazosulfonaryls of the Type $XC_6H_4SO_2N = P(OC_6H_4Y)_3$

X	Y	Yield %	M.p.	External form, solvent of crystallization	Composition of molecule	Found, %	Calc., %	Solubility*				
								alcohol	benzene	acetone	CCl_4	ligroin
p-CH_3O	H	84	85—86°	Prisms, ethanol	$C_{25}H_{22}O_6NSP$	P 5.97, 5.89	P 6.25	—	—	+	—	=
o-Cl	H	78	74—75	Prisms, ethanol	$C_{24}H_{19}O_5NSPCl$	P 6.05, 6.12	P 6.20	+	+	+ +	+	=
p-Br	H	90	87—88	Prisms, ethanol	$C_{24}H_{19}O_5NSPBr$	Br 14.89, 15.12	Br 14.68	+	+	+ +	+	—
p-CH_3O	p-NO_2	83	168—169	Needles, dioxane	$C_{25}H_{19}O_{12}N_4SP$	N 8.69, 8.55	N 8.88	—	—	+	—	=
o-Cl	p-NO_2	69	215—216	Prisms, dioxane	$C_{24}H_{16}O_{11}N_4SPCl$	N 8.71, 8.76	N 8.82	—	—	—	—	=

*Signs the same as in Table 1. All the substances were insoluble in boiling water.

TABLE 5

Trianilidophosphazosulfonaryls of the Type $XC_6H_4SO_2N = P(NHC_6H_5)_3$

X	Yield %	M.p.	Composition of molecule	% N	
				found	calc.
p-CH_3O	67	265—266°	$C_{25}H_{25}O_3N_4SP$	11.16, 11.01	11.38
o Cl	76	232—233	$C_{24}H_{22}O_2N_4SPCl$	10.71, 10.78	11.27
p-Cl	78	255—256	$C_{24}H_{22}O_2N_4SPCl$	11.58, 11.67	11.27
p-Br	81	258—259	$C_{24}H_{22}O_2N_4SPBr$	10.23, 10.13	10.35
p-F	89	244—245	$C_{24}H_{22}O_2N_4SPF$	11.89, 11.79	11.66
m CF_3	56	250—251	$C_{25}H_{22}O_2N_4SPF_3$	10.56, 10.63	10.56

along with the aniline hydrochloride. In these cases the mixture was filtered, the aniline hydrochloride was washed out with water, and the substances were recrystallized from alcohol.

Trichlorophosphazosulfonaryls (Table 2). A mixture of 0.1 mole of arylsulfonamide, 0.103 mole of PCl_5, and 10 ml of CCl_4 was boiled under reflux on an oil bath until evolution of hydrochloric acid stopped (about one hour). The solvent and residue of hydrogen chloride were removed in a vacuum. The reaction product crystallized out on cooling. The yield was quantitative. If pure starting substances were used, the trichlorophosphazosulfonaryl was sufficiently pure, and its melting point was not changed by recrystallization.

Acid dichlorides of arylsulfonamidophosphoric acids (Table 3). To a solution of 0.1 mole of trichlorophosphazosulfonaryls in 20 ml of benzene was added 0.1 mole of formic acid, and the mixture stood for a day. The precipitate of acid dichloride was filtered off and recrystallized from benzene.

Triaryloxyphosphazosulfonaryls (Table 4). A solution of 0.01 mole of trichlorophosphazosulfonaryls in 25 ml of benzene was slowly added to a suspension of 0.03 mole of sodium arylate in 20 ml of benzene. The mixture was heated on a water bath for one hour in the reaction with sodium phenolate, and for three to four hours in the reaction with sodium nitrophenolate. NaCl separated from the hot solution. Tri-p-nitrotriphenoxyphosphazosulfon-p-methoxyphenyl crystallized out when the benzene solution was cooled. In all the other cases, the benzene was distilled off in a vacuum and the remaining product was crystallized from the suitable solvent.

Trianilidophosphazosulfonaryls (Table 5). To a solution of 0.01 mole of trichlorophosphazosulfonaryl in 25 ml of benzene was added slowly, with cooling, a solution of 0.08 mole of aniline in 25 ml of benzene and the mixture was boiled for ten hours. The precipitated reaction product and the aniline hydrochloride were filtered off after cooling, the latter was washed out with water, and the residue was recrystallized from alcohol. The trianilidophosphazosulfonaryls were insoluble in water, benzene, CCl_4, acetone, and ligroin, and crystallized from alcohol in the form of very fine needles.

SUMMARY

When aniline acts on the acid chlorides of N-dichlorophosphinyl aryliminosulfonic acids, it yields the phenylamides of N-dianilidophosphinyl aryliminosulfonic acids, tautomeric with dianilidophosphinyl amides of N-phenylaryliminosulfonic acids, and similar in chemical properties to the arylamides of arylsulfonic acids and the dianilides of arylsulfonamidophosphoric acids.

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CARBON SUBOXIDE AND SOME OF ITS REACTIONS

VI. PYROLYTIC PREPARATION OF CARBON SUBOXIDE

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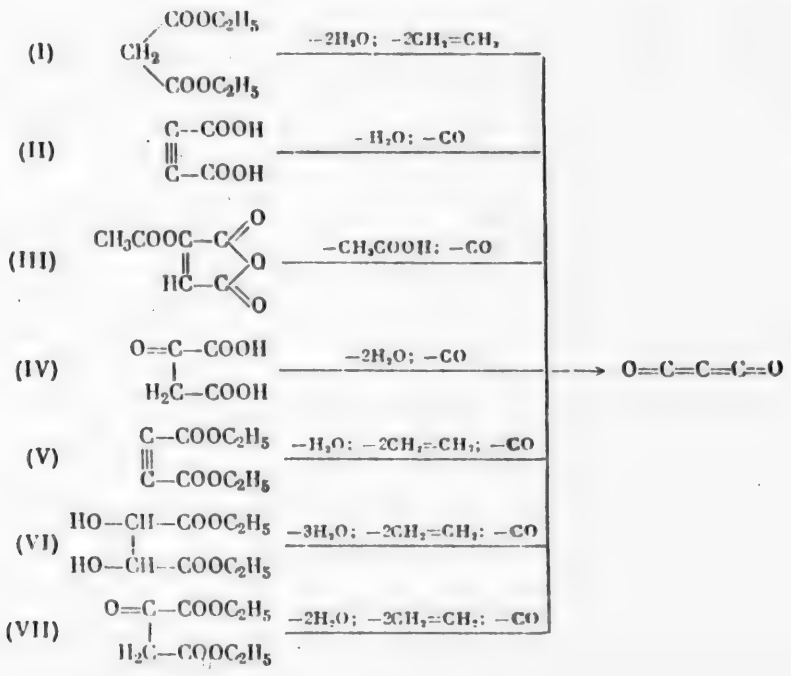
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1946-1950, June, 1960
Original article submitted March 3, 1959

It is known that carbon suboxide can be obtained by pyrolysis of diethylmalonate. This process occurs at 300-350° in the presence of phosphorus pentoxide and gives a yield which does not exceed 1-2% [1, 2]. Somewhat later it was shown that catalytic [3] and ordinary pyrolysis [4] of diacetyltartaric anhydride gives carbon suboxide in yields which vary between 30 and 40%. The pyrolytic preparation of carbon suboxide from diacetyltartaric anhydride has up to now been considered the most practically useful method.

In the present work we have studied the possibility of obtaining carbon suboxide by high-temperature pyrolysis of diethyl malonate and some derivatives of succinic acid.

It has been shown that carbon suboxide is formed by catalytic pyrolysis with different yields from diethyl malonate (I), acetylene dicarboxylic acid (II), acetoxymaleic acid anhydride (III), oxaloacetic acid (IV), and also from diethyl acetylene dicarboxylate (V), diethyl tartrate (VI), and diethyl oxaloacetate (VII) at tempera-


(I) CH2(COOC2H5)2 −2H2O; −2CH3=CH2
(II) HC≡C—COOH −H2O; −CO
(III) CH3COOC—C(=O)—HC—C(=O)—O −CH3COOH; −CO
(IV) O=C(COOH)—H2C—COOH −2H2O; −CO
(V) C2H5OOC—C≡C—COOC2H5 −H2O; −2CH3=CH2; −CO
(VI) HO—CH(COOC2H5)—CH(OH)—COOC2H5 −3H2O; −2CH3=CH2; −CO
(VII) O=C(COOC2H5)—H2C—COOC2H5 −2H2O; −2CH3=CH2; −CO
O=C=C=C=O

tures from 500 to 900°. In all these cases it was shown that the use of acetic anhydride solutions leads to a sharply increased yield of carbon suboxide. Under the conditions of the experiments, acetic acid was not pyrolyzed and was regenerated almost completely.

In the plan of our investigations we have suggested preparing radioactive carbon suboxide as a key substance for the synthesis of derivatives of malonic acid labeled with radiocarbon C^{14}.

We began by running the pyrolysis of diacetyltartaric anhydride labeled with C^{14} in the acetyl groups, since here at temperatures up to 850° isotope exchange and participation of the acetyl group in the formation of a molecule of carbon suboxide could occur, and we fully expected to obtain radioactive carbon suboxide. However, the carbon suboxide synthesized by this process was completely lacking in radioactivity.

It has been suggested in the literature that the pyrolysis of diacetyltartaric anhydride occurs by the following mechanism:

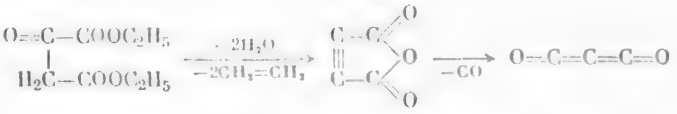
This interpretation was based on a remote analogy with the decomposition of oxaloacetates which when heated evolve carbon monoxide and on the hypothesis of the existence of carbon suboxide in the form of a lactone of the hypothetical hydroxypropargylic acid [5].

We did not set outselves the problem of explaining the mechanism of pyrolysis of diacetyltartaric anhydride. Nevertheless, the pyrolytic preparation of carbon suboxide from acetylene dicarboxylic acid and the above radiochemical experiment give us a basis for considering this reaction scheme very probable.

The comparatively low yield of carbon suboxide obtained in the pyrolysis of diethyl malonate (10%), acetylene dicarboxylic acid (3-5%), acetoxymaleic anhydride (8%), oxaloacetic acid (23%), diethyl acetylene dicarboxylate (up to 1%), diethyl tartrate (10%) lowers the preparative value of these reactions.

The pyrolysis of diethyl oxaloacetate gave the highest yield (up to 48%) of all the yet known pyrolytic methods for preparing carbon suboxide. Also the availability of diethyl oxaloacetate, which is easily synthesized from ethyl acetate and diethyl oxalate, will permit the use of this new method in practice.

We also pyrolyzed the (4-C^{14})-diethyl ester of oxaloacetic acid. As a result we obtained carbon suboxide with a molecular radioactivity about half the molecular radioactivity of the starting ester. Hence, the carbon skeletons of oxaloacetic acid (1-C^{12}) and (1-C^{14}) during decarboxylation share equally. This fact permits us to suggest that pyrolysis of diethyl oxaloacetate occurs analogously to the pyrolysis of diacetyltartaric anhydride through a stage of formation of the anhydride of acetylene dicarboxylic acid.



It is important to note that in carrying out all the experiments of this work we identified only the final product of the pyrolysis.

EXPERIMENTAL

Pyrolysis was carried out in a quartz tube with diameter 1.5 cm passing through a tubular furnace 32 cm long. Heating was regulated by a rheostat and was controlled by a thermopile which entered through a side opening of the furnace to the middle of the quartz tube.

The substance studied was introduced into the furnace from a dropping funnel with a pressure equalizer. The size of the yield of carbon suboxide was markedly affected by the evenness with which the product for pyrolysis was supplied; the rate of supply showed less effect. In every case we chose the optimum rate for supplying the substance for pyrolysis.

The pyrolyzate passed from the furnace into two successive flasks fitted with a high coil condenser cooled by water, where the acetic anhydride condensed (if the pyrolysis was carried out in acetic anhydride solution) along with the other liquids of the pyrolyzate. The carbon suboxide and other gases (such as carbon monoxide and ethylene) passed through two traps with coils placed in a cooling mixture. The carbon suboxide was bubbled through a capillary reaching to the bottom of a Wurtz flask into absolute ether cooled to −5°. In view of the known specific solubility of carbon suboxide in ether, passage of carbon suboxide from the first Wurtz flask was very slight, and this portion of the suboxide was practically completely absorbed in a second Wurtz flask.

The yield was calculated by the anilide method: five ml of ether solution of carbon suboxide was rapidly taken from the receiver and 10-20% solution of aniline in ether was added; the mixture was shaken for several minutes and after short standing the dianilide of malonic acid which precipitated was filtered off and dried to constant weight. Dianilide m.p. 227-228°.

Pyrolysis of diacetyltartaric anhydride. As is known, a method is described in the literature for obtaining carbon suboxide by pyrolysis of fused diacetyltartaric anhydride [4]. Since there are some experimental difficulties in getting the fusion, we undertook the pyrolysis of an acetic anhydride solution of diacetyltartaric anhydride. We showed that in this case the carbon suboxide was also not contaminated with carbomethylene, and the yield in separate experiments remained about the same.

We carried out pyrolysis of diacetyltartaric acid anhydride labeled with C^{14} on one of the acetyl groups. Radioactive acetic anhydride was obtained by reaction of 1.5 g (1-C^{14}) sodium acetate (total activity 0.5 mC) with the calculated amount of nonradioactive acetyl chloride [6]. Acetylation of tartaric acid by acetic anhydride occurred in the usual way [7]. The yield of sample was almost quantitative, the radioactivity was about 50% of that calculated on the acetic anhydride. Ten g of diacetyltartaric anhydride, specific radioactivity 24 mC /g), was placed in a wide test tube with a side arm in the upper part; the tubes were placed in an oil bath and the melt was evenly supplied to the furnace for pyrolysis by forcing it out the side tube with the help of mercury added through a dropping funnel during the course of one hour. Yield 37% (calculated as dianilide). The malonic acid dianilide was nonradioactive within the limits of error of the experiment.

We also carried out the pyrolytic process for getting carbon suboxide in a manner not described in the literature. Pyrolysis was carried out at different temperatures within the limits of temperature 500-900° and with different ratios of pyrolyzed substance and acetic anhydride. In a number of cases the suboxide was not obtained or was obtained in slight amount. Below we describe experiments with optimum conditions.

Pyrolysis of diethyl malonate. A mixture of 4.0 g of diethyl malonate with 25 ml of acetic anhydride was passed into the furnace for pyrolysis at 800° for one hour. Yield of C_3O_2 0.15 g (8%).

Pyrolysis of acetylene dicarboxylic acid. Acetylene dicarboxylic acid was synthesized by the usual method [8]. M.p. 180-181°.

a) A melt of 20 g of substance was passed through the furnace at 550° for 2.5 hr. Yield of C_3O_2 0.6 g (5%).

b) Ten g of acetylene dicarboxylic acid in 65 ml of acetic anhydride with passage through the furnace for 1.5 hr at 700° gave 0.96 g (16%) of carbon suboxide.

Pyrolysis of acetoxymaleic anhydride. Acetoxymaleic anhydride was obtained by the method in the literature [9]. M.p. 91-92°. Pyrolysis of the melted substance gave only a trace of carbon suboxide.

Ten g of acetoxymaleic anhydride in 60 ml of acetic anhydride was passed through the furnace at 600° for 1.5 hr. Yield of C_3O_2 0.37 g (8%).

Pyrolysis of oxaloacetic acid. Oxaloacetic acid was synthesized by the usual method [10]. M.p. 147°. Pyrolysis of the melt gave negative results.

Ten g of oxaloacetic acid in 60 ml of acetic anhydride at 650° (passed for 1.5 hr) gave 1.18 g (23%) of carbon suboxide.

Pyrolysis of diethyl acetylene dicarboxylate. Diethyl acetylene dicarboxylate was obtained by the known method [11]. B.p. 118-121° (20 mm). Pyrolysis of the acetic anhydride solution of diethyl acetylene dicarboxylate gave a very low yield (below 1%).

Pyrolysis of diethyl tartrate. Diethyl tartrate was obtained by reaction of alcohol with tartaric acid [12]. B.p. 153-155° (14 mm).

Eight g of diethyl tartrate in 55 ml of acetic anhydride at 850° (passed 1.5 hr) gave 0.25 g (10%) of carbon suboxide.

Pyrolysis of diethyl oxaloacetate. Diethyl oxaloacetate was obtained by condensing diethyl oxalate with ethyl acetate by the well known method [13]. B.p. 131-132° (25 mm).

Ten g of diethyl oxaloacetate in 70 ml of acetic anhydride was supplied to the furnace over two hours. The pyrolysis temperature was 850-880°. Yield of carbon suboxide 1.73 g (48%). This experiment was repeated several times. The yield of carbon suboxide varied between 42 and 48%.

Pyrolysis of diethyl ester of (4-C^{14})-oxaloacetic acid. The diethyl oxaloacetate was obtained as before. In the reaction we used ethyl acetate labeled with C^{14} in the ester group with a molecular radioactivity of 65 mC per mole.

Five g of diethyl oxaloacetate with a molecular radioactivity of 65 mC / mole was dissolved in 35 ml of acetic anhydride. The mixture was passed into the furnace at 850° for 40 min. Yield of C_3O_2 0.84 g, molecular radioactivity 36 mC / mole.

SUMMARY

1. We have shown that as a result of high temperature pyrolysis (500-900°) of acetoxymaleic anhydride, acetylene dicarboxylic acid, and oxaloacetic acid, and the diethyl esters of malonic, acetylene dicarboxylic, tartaric, and oxaloacetic acids carbon suboxide is formed. The use of acetic anhydride solutions of these substances, as a rule, markedly increases the yield of carbon suboxide.

2. Pyrolysis of acetic anhydride solutions of diethyl oxaloacetate is a practical method for preparing carbon suboxide, since in this case entirely satisfactory yields are obtained and the starting product is available.

3. By pyrolysis of the diethyl ester of (4-C^{14})-oxaloacetic acid we have synthesized carbon suboxide labeled with C^{14}.

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STUDIES IN THE SERIES OF ORGANIC SULFUR COMPOUNDS

VI. THE SYNTHESIS OF β-HYDROXYETHYLSULFONYL FLUORIDE N,N-DIMETHYLCARBAMATE

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1950-1954,
June, 1960
Original article submitted May 27, 1959

A study of the properties of β-halogen derivatives of sulfonyl chlorides and sulfonyl fluorides in the ethane and ethylene series showed [1] that the utilization of a substitution reaction for the halogen in the synthesis of several other derivatives (β-amino-, β-hydroxy) presented difficulties. Thus, β-halogen substituted alkane sulfonyl fluorides under the action of amines [2] split out a hydrogen halide intramolecularly and were not converted to the corresponding β-amino derivatives. Even iodomethane- and β-chlorovinylsulfonyl fluorides, which could not undergo intramolecular dehydrohalogenation, were unsuitable as starting compounds for the synthesis of amino derivatives.

Although the fluorine atom in alkane sulfonyl fluorides is considerably more firmly bound to sulfur than is chlorine in the sulfonyl chlorides,* attempts to use this property in the reaction of dimethylamine with iodomethane- and β-chlorovinylsulfonyl fluorides were unsuccessful. Also, it is difficult to obtain β-hydroxy derivatives of ethanesulfonyl chloride, ethanesulfonyl fluoride, and their corresponding esters.

It appeared interesting to obtain amino substituted ethanesulfonyl fluorides according to the scheme

$$(CH_3)_2NCOOCH_2CH_2SO_2F \xrightarrow{-CO_2} (CH_3)_2NCH_2CH_2SO_2F$$

The synthesis of the starting ester of β-hydroxyethanesulfonyl fluoride and N,N-dimethylcarbamic acid was carried out in the following way:

$$(CH_3)_2NCOCl \xrightarrow{HOCH_2CH_2SCN} (CH_3)_2NCOOCH_2CH_2SCN \xrightarrow[H_2O]{Cl_2}$$
$$\longrightarrow [(CH_3)_2NCOOCH_2CH_2SO_2Cl] \xrightarrow{KF} (CH_3)_2NCOOCH_2CH_2SO_2F$$

The resulting sulfonyl fluoride was a nondistillable oil which, judging by the results of analysis (increased values for fluorine and hydrogen content), tended toward decarboxylation.

The starting N,N-dimethyl-β-thiocyanatoethylurethane is an unstable substance which decomposes violently even at about 80°. Its methiodide is more stable so that it can be decarboxylated, and under the conditions which we have found, can avoid a more deep-seated spontaneous decomposition.

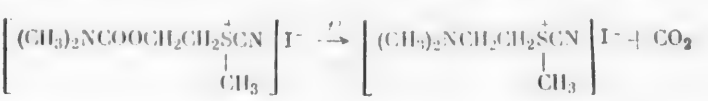
By heating N,N-dimethyl-β-thiocyanatoethyl urethane with methyl iodide in methanol we obtained the methiodide.

$$(CH_3)_2NCOOCH_2CH_2SCN \xrightarrow{CH_3I} \left[(CH_3)_2NCOOCH_2CH_2\overset{+}{S}(CH_3)CN\right]\bar{I}$$

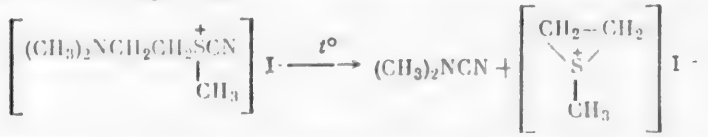
*This was shown in special experiments on the reaction of triethylamine with methanesulfonyl chloride and methanesulfonyl fluoride.

It is interesting to note that the formation of a sulfonium methiodide leads to such strong polarization of the S-CN bond that the resulting compound in water solution gives a positive reaction for the cyanide ion and does not give the reaction for the thiocyanate ion which is characteristic of the starting thiocyanate.

N,N-Dimethyl-β-thiocyanatoethyl urethane methiodide when heated in a stream of nitrogen to 90-100° can decarboxylate, giving the methiodide of N,N-dimethyl-β-thiocyanatoethylamine.•



N,N-Dimethyl-β-thiocyanatoethylamine methiodide can exchange an atom of iodine with a cyanide group by the action of silver cyanide and cannot add a second molecule of methyl iodide when it is heated with this for a long time in methanol. This finds confirmation in the fact reported in the literature [3] that it is not possible to obtain a bis-quaternary ammonium salt of N,N'-tetramethylmethylenediamine. Heating the methiodide in a sealed ampule leads to its decomposition.



Thus we have succeeded in carrying out the decomposition of the methiodide of N,N-dimethyl-β-thiocyanatoethyl urethane in a stepwise manner with isolation of N,N-dimethyl-β-thiocyanatoethylamine methiodide as the product of the first step in the decomposition. If N,N-dimethyl-β-thiocyanatoethyl urethane reacts with methyl iodide in a sealed tube, then besides the formation of the methiodide (with heating or in the cold) there is spontaneous decomposition of the substance and it is possible to isolate from the reaction products only dimethylcyanamide, ethylene sulfide methiodide, and carbon dioxide. It follows from this that the intermediate compounds in the synthesis of esters of β-hydroxyethanesulfonyl fluoride are thermally unstable substances which cannot undergo distillation so that they must be purified by precipitation methods and cannot be characterized by the usual constants.

Further action of chlorine in an aqueous medium with illumination converts N,N-dimethyl-β-thiocyanatoethyl urethane into the corresponding sulfonyl chloride, which is converted in the usual way into the sulfonyl fluoride by heating with anhydrous potassium fluoride. Thus, in the present work we have carried out the synthesis of the first example of a sulfonyl fluoride which contains an esterified hydroxygroup in the β-position.

EXPERIMENTAL

N,N-Dimethyl-β-thiocyanatoethyl urethane (I). One hundred g of ethylene chlorohydrin and 132 g of potassium thiocyanate were heated to 60-80° with stirring for 18 hr and filtered from the precipitate.

Analysis of the filtrate showed that it contained about 50% β-thiocyanatoethanol. We treated 88 g of the mixture with 117 g of N,N-dimethylcarbamyl chloride (calculated on pure ethylene chlorohydrin) in 110 g of triethylamine. After separation of the precipitated ammonium salt, we distilled off from the filtrate the excess N,N-dimethylcarbamyl chloride and also the N,N-dimethyl-β-chloroethyl urethane which was formed, at 80-84° (9 mm).•• The residue was extracted with acetone and precipitated with ether. A viscous, dark-red mass precipitated.

Found %: C 41.73, 41.37; H 5.85, 5.55; N 16.01, 16.03. $C_6H_{10}O_2N_2S$. Calculated %: C 41.36; H 5.78; N 16.07.

It was unstable and decomposed on long keeping with evolution of bubbles of gas even in cold solutions in water. The aqueous solution gave a positive reaction for thiocyanate ion with silver nitrate and ferric chloride.

•Here, as in the previous case, the position of salt formation is the sulfur atom, which is confirmed by the positive reaction for the cyanide ion.

••It is very important that the temperature should not exceed that given, since violent decomposition of the substance may begin with ejection of the mixture from the flask.

N,N-Dimethyl-β-fluorosulfonylethyl urethane (II). We suspended 47.6 g of N,N-dimethyl-β-thiocyanatoethyl urethane in 250 ml of water and with energetic stirring and illumination with a 200 watt lamp we chlorinated it at 15-20° until chlorine passed through. The thick, light yellow oil which precipitated was separated from the water and extracted with benzene; the benzene extract was dried by heating with calcium chloride. After distillation of the benzene, the residue was a viscous substance with an odor characteristic of sulfonyl chlorides, insoluble in ether. The N,N-dimethyl-β-chlorosulfonylethyl urethane was heated with an excess of freshly ignited, finely ground potassium fluoride to 60°. Then the mixture was extracted with acetone, the solvent was removed, and we obtained (II) in the form of a dark-red oil, soluble in water.

Found %: C 30.46, 30.76; H 5.17, 5.54; F 10.38, 10.27. $C_5H_{10}O_4NSF$. Calculated %: C 30.15; H 5.06; F. 9.53.

Action of methyl iodide on (I) in a sealed tube. We heated 5.22 g of (I) in a sealed tube with 4.23 g of methyl iodide for 16 hr on a water bath. When the cooled tube was opened we found considerable pressure and the contents foamed strongly. Washing with acetone gave light yellow crystals with m.p. 180°, insoluble in ether and acetone, but easily soluble in water.

Found %: C 17.09, 17.11; H 3.17, 3.32; S 16.17, 16.27. C_3H_7SI. Calculated %: C 17.83; H 3.49; S 15.84.

The properties and analysis of this substance identified it as ethylene sulfide methiodide [4].

By distillation of the acetone solution we isolated a substance with b.p. 160-163° (760 mm) which crystallized in the receiver and was identified by its constants as N,N-dimethylcyanamide [5]. In an analogous experiment at room temperature for 15 days we obtained the same result.

Action of methyl iodide on (I) in methanol solution. Ten g of (I) and 90 g of methyl iodide in 25 ml of methanol were heated for 18 hr. After distillation of excess methyl iodide and the solvent, the remaining oil was dissolved in acetone, the solution was filtered and cold acetone was distilled off in a vacuum. The residue was washed three times by decantation with ether and kept in the cold in a vacuum desiccator for 24 hr. The dark-red, viscous liquid, soluble in water and acetone and insoluble in ether, was kept for a long time without visible change; the aqueous solution gave a positive reaction for iodide and cyanide and did not give a reaction for thiocyanate ion.

Found %: C 26.90, 27.37; H 4.38, 4.41; N 9.25, 9.21; S 9.57, 9.69. $C_7H_{13}O_2N_2SI$. Calculated %: C 26.58; H 4.14; N 8.85; S 10.12.

Heating the methiodide of (I) in an atmosphere of nitrogen to about 90-100° caused decarboxylation. The carbon dioxide was collected quantitatively in alkali. The residue was analyzed without further purification.

Found %: C 26.60, 26.38; H 5.26, 5.19; N 9.96, 10.08; S 11.25, 11.67. $C_6H_{13}N_2SI$. Calculated %: C 26.47; H 4.81; N 10.29; S 11.76.

The resulting substance was heated for ten hours with methyl iodide in methanol solution. There was no formation of a crystalline reaction product. The reaction mixture was then sealed in an ampule and heated at first on a water bath and then on a glycerine bath for five days. Again no formation of crystals was observed. When the ampule was opened there was considerable pressure and the contents foamed. After the usual treatment we obtained crystals of ethylene sulfide methiodide and dimethylcyanamide, identified as described above.

Action of silver cyanide on the methiodide of (I). To a solution of 1 g of methiodide of (I) in anhydrous acetone was added 0.42 g of silver cyanide weighed out in acetone; the solution at once decolorized and a characteristic precipitate of silver iodide came down. After filtration, a white crystalline precipitate was isolated from the filtrate, which did not dissolve in alcohol and ether, deliquesced strongly in air, contained no iodine and perhaps was the product of replacement of an iodine atom in the methiodide of (I) by a CN group; however, we were unable to isolate an analytically pure preparation.

Reaction of triethylamine with methanesulfonyl chloride and methanesulfonyl fluoride. To a cooled ether solution of methanesulfonyl chloride we added dropwise an ether solution of triethylamine. The precipitate was washed with ether and dried. We obtained triethylmethanesulfonyl ammonium chloride, m.p. 176-180°.

Found %: Cl 16.2, 16.0. $C_7H_{18}O_2NSCl$. Calculated %: Cl 16.43.

Methanesulfonyl fluoride, only after boiling for many days with triethylamine in ether solution, gave an oily triethylmethanesulfonyl ammonium fluoride.

Found %: F 9.0, 9.2. $C_7H_{18}O_2NSF$. Calculated %: F 9.54.

Action of diethylamine on iodomethanesulfonyl fluoride. To 10 g of iodomethanesulfonyl fluoride in absolute ether was added 2.01 g of dimethylamine at −75°. The mixture was stirred for 40 min with cooling and the temperature was gradually brought to 0°. Then 9 ml of 1% sulfuric acid solution was added and the precipitate dissolved. The ether layer was washed with 1% sulfuric acid, water, 20% sodium chloride, and was dried with ignited sodium sulfate. When the solvent was evaporated there remained a heavy brown oil which did not contain fluorine and did contain iodine; it was not further investigated.

SUMMARY

1. We have synthesized N,N-dimethyl-β-hydroxyethylsulfonyl fluoride carbamate.

2. We have shown that N,N-dimethyl-β-thiocyanatoethyl urethane methiodide can be decarboxylated into N,N-dimethyl-β-thiocyanatoethylamine methiodide, and when it is heated in a sealed tube it is decomposed to dimethylcyanamide, ethylene sulfide methiodide, and carbon dioxide.

3. We have noted a weakening of the S-CN bond in the thiocyanates when they form methiodides.

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INVESTIGATIONS IN THE FIELD OF ALKOXYSILANES

XV. THE CLEAVAGE OF HEXAALKYLDISILOXANES BY PHENOLS A NEW METHOD OF SYNTHESIS OF TRIALKYLSILOXY DERIVATIVES OF AROMATIC HYDROCARBONS

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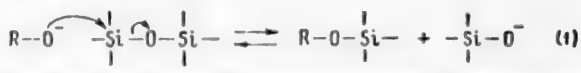
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1955-1958, June, 1960
Original article submitted June 11, 1959

In the preceding communication [1] the possibility was shown of cleavage of the siloxane bond by alcohols in presence of alkaline catalysts with formation of alkoxysilanes. The initial step in this nucleophilic reaction is the coordination of the alkoxyl ion with an atom of silicon due to the entry of an unshared pair of 2p oxygen electrons into the vacant 3d orbital of silicon.



(1)

It was of interest to bring about the cleavage of organosiloxanes not by alcohols but by phenols. In view, however, of the acidic properties of phenols it had been expected that the reaction would be impossible in presence of an alkaline catalyst. The experiments that were instituted did indeed show that phenols practically do not react with hexaalkyldisiloxanes in presence of KOH.

Since the polar disiloxane molecule contains a nucleophilic center (oxygen), apart from an electrophilic center (silicon), it seemed that cleavage of the siloxane bond might be realized by phenols of the electrophilic type with the help of strong protonic or aprotonic acids as catalysts. Numerous examples of the susceptibility of the Si—O—Si bond to cleavage by strong acids have been reported. The possibility has been noted [2] of cleavage of hexaalkyldisiloxanes even by the relatively weak phosphoric acid in presence of catalytic quantities of H_2SO_4 or $ZnCl_2$.

Experimental data fully confirmed these possibilities. It was found that mono- and polyhydric phenols cleave hexaalkyldisiloxanes in presence of strong protonic or aprotonic acids under conditions of continuous azeotropic distillation of the water of reaction

$$2Ar(OH)_n + nR_3SiOSiR_3 \overset{H^+}{\rightleftarrows} 2Ar(OSiR_3)_n + nH_2O.$$

Ar is a n-valent aromatic radical.

The best catalysts for this reaction are aromatic sulfonic acids, in particular benzenesulfonic acid. Sulfuric acid and zinc chloride were less effective.

In this way it was possible to cleave hexamethyldisiloxane with phenol, all of the three cresols, dihydroxybenzenes, p-chlorophenol and phloroglucinol. Yields of trimethylsiloxy derivatives of benzene, toluene and chlorobenzene, physical properties and analytical data are set forth in the table. Six of these compounds were previously unknown.

Physical Properties, Analytical Data and Yields of Trimethylsiloxy Derivatives of Benzene, Toluene, and Chlorobenzene

Compound	Uncorrected boiling point (pressure in mm)	d_4^{20}	n_D^{20}	Empirical formula	% Si		% C		% H		Yield of unpurified compound (in %)
					found	calc.	found	calc.	found	calc.	
$C_6H_5OSi(CH_3)_3$ (Trimethylsiloxy)benzene[a]	178° (760)	0.9267	1.4780	$C_9H_{14}OSi$	16.49, 16.30	16.89	65.00, 64.80	65.00	8.44, 8.53	8.49	72
$1,2\text{-}CH_3C_6H_4OSi(CH_3)_3$ 1-Methyl-2-(trimethylsiloxy)benzene*	192 (760), 77 (12)	0.9287	1.4830	$C_{10}H_{16}OSi$	—	15.58	66.99, 66.99	66.61	9.00, 9.11	8.94	88
$1,3\text{-}CH_3C_6H_4OSi(CH_3)_3$ 1-Methyl-3-(trimethylsiloxy)benzene*	113 (79)	0.9256	1.4791	$C_{10}H_{16}OSi$	15.61, 15.79	15.58	66.89, 66.68	66.61	8.99, 9.09	8.94	88
$1,4\text{-}CH_3C_6H_4OSi(CH_3)_3$ 1-Methyl-4-(trimethylsiloxy)benzene*	59 (1)	0.9252	1.4790	$C_{10}H_{16}OSi$	15.88, 15.54	15.58	66.72, 66.55	66.61	9.04, 9.11	8.94	42 **
$1,4\text{-}ClC_6H_4OSi(CH_3)_3$ 1-Chloro-4-(trimethylsiloxy)benzene[b]	214 (758)	1.0920	1.4842	$C_9H_{13}ClOSi$	13.80, 13.62	13.99	53.72, 53.98	53.85	6.71, 6.83	6.53	59
$1,2\text{-}C_6H_4(OH)OSi(CH_3)_3$ 2-(Trimethylsiloxy)phenol*	218 (776), 97 (2)	0.9847	1.4570	$C_9H_{14}O_2Si$	16.49, 16.62	15.41	58.82, 58.52	59.39	8.15, 8.38	7.74	87
$1,3\text{-}C_6H_4[OSi(CH_3)_3]_2$ 1,3-Bis-(trimethylsiloxy)benzene[c]	208 (776), 116 (7)	0.9471	1.4743	$C_{12}H_{22}O_2Si_2$	22.06, 22.27	22.07	56.68, 56.39	56.64	8.73, 8.79	8.71	59 **
$1,4\text{-}C_6H_4[OSi(CH_3)_3]_2$ 1,4-Bis-(trimethylsiloxy)benzene*	216 (776), M.p. 46° 114 (4)	—	—	$C_{12}H_{22}O_2Si_2$	22.16, 22.27	22.07	56.95, 57.01	56.64	8.66, 8.56	8.71	28 **
$1,3,5\text{-}C_6H_3[OSi(CH_3)_3]_3$ 1,3,5-Tris-(trimethylsiloxy)benzene*			1.4675	$C_{15}H_{30}O_3Si_3$	24.32, 24.48	24.59	52.58, 52.65	52.58	9.15, 9.30	8.82	69

Notes: Literature data: a) B.p. 68-69° (13 mm), d_4^{20} 0.9256, $n^{20}D$ 1.4787 [4]; B.p. 181.9-192.4° (742 mm), d_4^{20} 0.9256, $n^{20}D$ 1.4782 [3]. B.p. (14 mm), b) d_4^{25} 1.042, $n^{25}D$ 1.4923 [5]; % Cl: Found 17.51; 17.45 calc. 17.68. c) B.p. 239° 117-119° (15 mm) [6]; b.p. 237-240° (740 mm), 154-159° (100 mm), d_4^{20} 0.950, $n^{20}D$ 1.47 48.

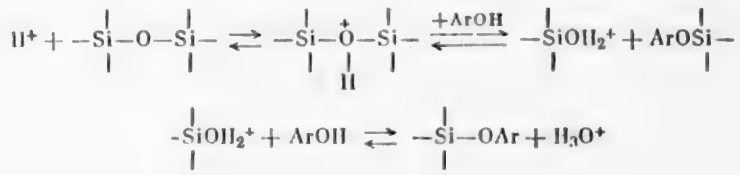
*New compound.

**Yield of pure substance.

It should be noted that the main product of reaction of a considerable excess of hexamethyldisiloxane with pyrocatechol is not 1,2-bis-(trimethylsiloxy)benzene but trimethylsiloxyphenol. The presence of an unsubstituted hydroxyl group in the latter is confirmed by the OH valence vibration band near 3550 cm^{-1} observed in its spectrum, as well as by analytical data. Steric hindrance is evidently responsible for the difficulty of introduction of the second hydroxyl into reaction.

The reaction is a new and convenient route to mono- and polytrialkylsiloxy derivatives of aromatic hydrocarbons. Previously these compounds had been obtained by interaction of the corresponding phenols with trialkylchlorosilanes [3-6], trialkylalkoxysilanes [4] or trialkylsilanes [7].

The mechanism of reaction of hexaalkyldisiloxanes with phenols may be represented in the following manner:



EXPERIMENTAL

Preparation and purification of hexamethyldisiloxane have already been described [8]. Starting phenols—commercial products—were further purified by distillation or sublimation in vacuo. Benzenesulfonic acid was used in the form of the monohydrate (m.p. 45°), obtained by recrystallization of the commercial product from benzene.

Procedure of syntheses. All syntheses were carried out in an apparatus of all-glass construction comprising a round-bottomed flask joined via a water-removal trap to a reflux condenser. In the flask were placed 0.2 mole of the phenol, 1.0 g of benzenesulfonic acid monohydrate and double the required quantity of hexamethyldisiloxane.*

The mixture was boiled vigorously until water ceased to separate in the trap. Unreacted hexamethyldisiloxane was distilled off and the reaction product isolated by distillation in vacuo. For elimination of contaminating original phenol and partial ethers, it was dissolved in benzene and treated with metallic sodium at room temperature for 1-2 days. The solution was filtered, the benzene distilled off, and the pure substance isolated by redistillation in vacuo.

For the purpose of illustration we now describe the synthesis of trimethylsiloxybenzene. A mixture of 65 g (0.4 mole) of hexamethyldisiloxane, 18.8 g (0.2 mole) of phenol and 1 g of benzenesulfonic acid was boiled under a reflux condenser fitted with a water-removing trap until water ceased to separate in the trap (3 ml after 20 hr). Fractional distillation of the reaction mixture gave 39 g of unreacted hexamethyldisiloxane with b.p. 98-103° and 24.0 g (72%) of trimethylsiloxybenzene with b.p. 176-178°, $n^{20}D$ 1.4800. A solution of the latter in 50 ml of dry benzene was stood for 24 hr over sodium wire, filtered and distilled.

Performance of the same reaction in presence of 2 g of conc. H_2SO_4 or 1 g of anhydrous $ZnCl_2$ led to yields of trimethylsiloxybenzene of 50 and 15%, respectively.

SUMMARY

A method was developed for synthesis of mono- and polytrialkylsiloxy derivatives of aromatic hydrocarbons, based on the cleavage of hexaalkyldisiloxanes by mono- and polyhydric phenols in presence of acid catalysts (preferably aromatic sulfonic acids). This method gave eight full trimethylsilyl ethers of phenols, all of the isomeric cresols, p- and m-dihydroxybenzenes, p-chlorophenol and phloroglucinol, also the partial ether of pyrocatechol. Six of these compounds were previously unknown.

A mechanism of the reaction is put forward.

* The excess of hexamethyldisiloxane serves simultaneously as a solvent for the azeotropic distillation of the water.

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*Original Russian pagination. See C. B. translation.

DIPHENYLALKOXY- AND DIPHENYLAROXYPHOSPHAZOSULFONARYLS

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1958-1960,
June, 1960
Original article submitted May 29, 1959

Diphenylchlorophosphazosulfonaryls are acid chlorides of arylsulfonimidodiphenylphosphinic acids and react easily with water, alcohols, amines, and other compounds containing an active hydrogen atom. They react with even greater facility with sodium alkoxides and phenoxides to form respectively, diphenylalkoxyphosphazosulfonaryls (esters of arylsulfonimidodiphenylphosphinic acids) (I, R = Al) and diphenylaroxyphosphazosulfonaryls (II, R = Ar).

$$(C_6H_5)_2ClP{=}NSO_2Ar \xrightarrow[-NaCl]{+RONa} (C_6H_5)_2(RO)P{=}NSO_2Ar,$$

Diphenylalkoxyphosphazosulfonaryls (II) are crystalline, neutral substances, insoluble in water, ether and carbon tetrachloride, readily soluble in acetone and hot alcohol. They crystallize easily from alcohol as well-formed, fine prisms. They are not hydrolyzed by water or 50% alcohol even after very prolonged heating. They are also not hydrolyzed by aqueous sodium hydroxide, evidently due to their insolubility in water. However hydrolysis goes very easily on heating in 0.1 N aqueous alcoholic solution of sodium hydroxide with formation of sodium salts of arylsulfonamidodiphenylphosphinic acids $ArSO_2N = P(C_6H_5)_2(ONa)$. They are hydrolyzed by 0.1 N aqueous alcoholic solution of hydrochloric acid with formation of arylsulfonamidodiphenylphosphinic acids.

Similarly to (I), diphenylchlorophosphazosulfonaryls react with sodium phenoxides to give diphenylphenoxyphosphazosulfonaryls (II).

Like (I), diphenylphenoxyphosphazosulfonaryls (II) are colorless, crystalline substances; they are insoluble in water and ether, easily soluble in benzene and hot alcohol. They crystallize nicely from alcohol in the form of fine prisms.

They are extremely stable in water or aqueous solutions of alkalies, in which they are insoluble. They remain unchanged in these media even after heating for an hour . However, they are hydrolyzed rapidly and quantitatively by aqueous alcoholic sodium hydroxide solution.

EXPERIMENTAL

Diphenylalkoxy- and diphenylphenoxyphosphazosulfonaryls. To a solution of sodium alkoxide, prepared from 0.0015 g-atom of sodium and 10 ml of the appropriate alcohol, was added a solution of 0.0015 mole of diphenylchlorophosphazosulfonaryl in 10 ml of benzene from a dropping funnel with stirring. The benzene and alcohol were carefully distilled off in vacuo on a water bath, and to the viscous, oily residue was added 40-50 ml of water. The mixture was stirred. A crystalline solid at once came out and was separated, washed with water and crystallized.

Diphenylphenoxyphosphazosulfonaryls were prepared by mixing equimolar quantities (0.0015 mole) of sodium phenoxide and diphenylchlorophosphazosulfonaryl dissolved in 10 ml of benzene. Isolation and purification were carried out as previously.

TABLE 1

Diphenylalkoxyphosphazosulfonaryls $(C_6H_5)_2(AlkO)P = NSO_2Ar$ (I)

Alk	Ar	Yield (in %)	Melting point	Found %OAlk	Empirical formula	Calc. %OAlk
CH_3	C_6H_5	63.3	109–110°	8.30	$C_{19}H_{18}O_3NSP$	8.35
CH_3	o-$CH_3C_6H_4$	75.1	123–124	8.01	$C_{20}H_{20}O_3NSP$	8.05
CH_3	p-$CH_3C_6H_4$	70.8	112–113	8.04	$C_{20}H_{20}O_3NSP$	8.05
CH_3	β-$C_{10}H_7$	68.5	118–119	7.33	$C_{23}H_{20}O_3NSP$	7.36
CH_3	p-$NO_2C_6H_4$	66.6	170–172	7.40	$C_{19}H_{17}O_5N_2SP$	7.45
C_2H_5	C_6H_5	71.5	117–118	11.42	$C_{20}H_{20}O_3NSP$	11.69
C_2H_5	o-$CH_3C_6H_4$	74.8	122–123	11.38	$C_{21}H_{22}O_3NSP$	11.28
C_2H_5	p-$CH_3C_6H_4$	75.0	96–97	11.40	$C_{21}H_{22}O_3NSP$	11.28
C_2H_5	β-$C_{10}H_7$	66.2	104–105	10.24	$C_{24}H_{22}O_3NSP$	10.34
C_2H_5	p-$NO_2C_6H_4$	66.2	49–50	10.27	$C_{20}H_{19}O_5N_2SP$	10.46

TABLE 2

Diphenylphenoxyphosphazosulfonaryls $(C_6H_5)_2(C_6H_5O)P = NSO_2Ar$ (II)

Ar	Yield (in %)	Melting point	Found %N	Empirical formula	Calc. %N
C_6H_5	84.6	113–114	3.40	$C_{24}H_{20}O_3NSP$	3.23
o-$CH_3C_6H_4$	86.0	139–140	3.18	$C_{25}H_{22}O_3NSP$	3.15
p-$CH_3C_6H_4$	85.2	125–126	3.17	$C_{25}H_{22}O_3NSP$	3.15
β-$C_{10}H_7$	78.2	130–132	2.95	$C_{28}H_{22}O_3NSP$	2.89

Hydrolysis of diphenylalkoxy- and diphenylphenoxyphosphazosulfonaryls. To 0.001 mole of (I) or (II) was added 12 ml of 0.002 N aqueous alcoholic sodium hydroxide (10 ml of C_2H_5OH + 2 ml of 1 N aqueous NaOH) and the mixture heated to the boil for an hour. Arylsulfonamidodiphenylphosphinic acids came down when the hydrolyzate was acidified until the mass had an acid reaction. Yield nearly quantitative.

SUMMARY

Diphenylalkoxy- and diphenylphenoxyphosphazosulfonaryls were synthesized by reaction of diphenylchlorophosphazosulfonaryls with sodium alkoxides and phenoxides. Their hydrolysis was also effected.

DIPHOSPHONATES

III. SYNTHESIS OF O- AND S-BISPHOSPHONATES

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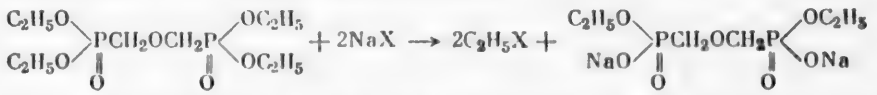
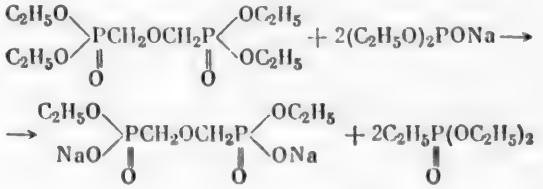
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1960-1964.
June, 1960
Original article submitted May 26, 1959

With respect to their properties and the methods of their preparation, substances of the type of $[(RO)_2P(O)-CH_2)_n]_2O$ and $[(RO)_2P(O)(CH_2)_n]_2S$ are very similar to the previously considered diphosphonates [1, 2]. These compounds have scarcely been studied. At the present time we are aware of only bis-(diethylphosphono)dimethyl ether, obtained by alkylation of triethyl phosphite and sodium diethyl phosphite by dichloro- and dibromomethyl ethers [3].

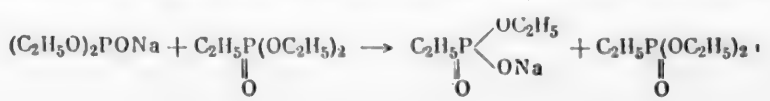
Preparation of a diphosphonate by alkylation of sodium diethyl phosphite by dichloro- and dibromodimethyl ethers introduces great difficulties in connection with isolation of the reaction product due to formation of a finely dispersed solid which can be eliminated only by centrifuging or decantation. The neutral ester of diphosphonic acid is not isolated if distillation is performed without previous separation of the precipitate. This has been explained by the circumstance [3] that sodium chloride or bromide reacts with the diphosphonate which is thereby converted into the disodium salt of the ester of diphosphonic acid.



Such reactions are known to proceed only at high temperatures (about 200°) at which sodium chloride does not usually react [4]. Moreover the formation of ester-salts in the reaction in question also takes place at fairly low temperatures (70-80°) so that it is impossible to attribute it to reaction of sodium chloride with diphosphonate. This last fact is easy to understand in the light of our investigations [1, 2, 5] of the alkylation of sodium dialkyl phosphites by neutral esters of alkylphosphinic and diphosphonic acids which usually takes place during preparation of phosphonates and diphosphonates by the Michaelis–Becker reaction. In the present case ester-salts may be considered to be formed by the following mechanism:



In addition to the ester-salt of the diphosphonate, there is also formed a certain amount of salt of ester of ethylphosphinic acid due, it may be suggested, to alkylation of sodium diethyl phosphite by ethyl phosphonate.



Formula	Boiling point (pressure in mm)	Viscosity at 20° (centipoises)	d_4^{20}	n_D^{20}	MR calc.	MR found
(iso-$C_3H_7O)_2P(O)CH_2OCH_2P(O)(OC_3H_7$-iso)$_2$	171–172° (1.75)	32	1.0770	1.4329	90.23	90.31
(n-$C_4H_9O)_2P(O)CH_2OCH_2P(O)(OC_4H_9$-n)$_2$	200–202° (0.4)	27	1.0616	1.4425	108.60	107.40
(iso-$C_3H_7O)_2P(O)CH_2CH_2OCH_2CH_2P(O)(OC_3H_7$-iso)$_2$	154–155° (0.7)	26.4	1.0506	1.4330	99.47	99.54
(n-$C_4H_9O)_2P(O)CH_2CH_2OCH_2CH_2P(O)(OC_4H_9$-n)$_2$	210–211° (0.6)	20.8	1.0212	1.4439	117.94	119.20
$(C_2H_5O)_2P(O)CH_2SCH_2P(O)(OC_2H_5)_2$	179–180° (2)	—	1.1950	1.4696	78.03	77.96
(iso-$C_3H_7O)_2P(O)CH_2SCH_2P(O)(OC_3H_7$-iso)$_2$	164–165° (0.4)	29	1.1019	1.4548	96.65	96.10
(n-$C_4H_9O)_2P(O)CH_2SCH_2P(O)(OC_4H_9$-n)$_2$	230–232° (2)	24.8	1.0786	1.4628	115.13	113.98
(iso-$C_3H_7O)_2P(O)CH_2CH_2SCH_2CH_2P(O)(OC_3H_7$-iso)$_2$	150–151° (0.8)	25.2	1.0608	1.4532	105.89	106.67
(n-$C_4H_9O)_2P(O)CH_2CH_2SCH_2CH_2P(O)(OC_4H_9$-n)$_2$	202–204° (0.6)	27.5	1.0314	1.4509	124.36	123.87

We also observed formation of esters of alkylphosphinic and diphosphonic acids in preparation of other diphosphonates by reaction of sodium dialkyl phosphites with dihaloethers and sulfides. In a number of cases, as in the preparation of ethylenediphosphonates [2], secondary alkylation reactions can be suppressed and in turn, the yield of neutral ester of diphosphonic acid increased by changing the sequence of addition of reactants and operating at a suitable temperature.

In the present work we studied reactions of sodium dialkyl phosphites with dichlorodimethyl and β,β'-dichlorodiethyl ethers, as well as with dichlorodimethyl and β,β'-dichlorodiethyl sulfides. In all cases, neutral esters of the respective diphosphonic acids were obtained. Difficulties in isolation of these products associated with formation of a precipitate are easily eliminated by addition to the reaction mixture of water in quantity sufficient for dissolution of the salt and by washing of the organic salt with dilute alkali and water. After this treatment, the diphosphonates usually distil without decomposition. However, if decomposition still takes place, the distillation must be performed over a small quantity (3-5% of the weight of the product) of anhydrous sodium or potassium carbonate.

O- and S-bisphosphonates are high-boiling, thermally stable, viscous liquids, insoluble or poorly soluble in water and readily soluble in organic solvents. Some of these substances, like compounds of the type of $(CH_2)_n[P(O)(OR)_2]_2$ [6], may be tested out as thermostable lubricating oils, oil additives plasticizers or hydraulic fluids. The properties of the prepared compounds are set forth in the table.

EXPERIMENTAL

Bis-(diisopropylphosphono)dimethyl ether. To the sodium salt of diisopropylphosphorous acid, obtained from 6 of sodium and 44 g of diisopropyl phosphite in 150 ml of anhydrous toluene, was added 27 g of dibromodimethyl ether dropwise with stirring, at such a speed that the temperature of the reaction mixture remained at 40-50°. For completion of the reaction the mixture was heated at the same temperature for 30 min; it was then cooled and water was added to dissolve the precipitate. The organic layer was washed with 5% alkali solution, then with water and dried over magnesium sulfate. Distillation gave 36 g (70%); b.p. 171-172° (1.75 mm).

Found %: P 16.70, 16.89. $C_{14}H_{32}O_7P_2$. Calculated %: P 16.55.

Bis-(dibutylphosphono)dimethyl ether. From 8.5 g of sodium, 72 g of dibutyl phosphite and 37.8 g of dibromodimethyl ether in 150 ml of anhydrous benzene under conditions similar to those for the synthesis of the isopropyl analog. Yield 55 g (69.3%), b.p. 200-202° (0.4 mm).

Found %: P. 14.66, 14.74. $C_{18}H_{40}O_7P_2$. Calculated %: P 14.40.

Bis-(diisopropylphosphono)diethyl ether. To the sodium salt of diisopropylphosphorous acid, prepared from 15 g of sodium and 108.5 g of diisopropyl phosphite in 400 ml of dry toluene, was added 46.5 g of β,β'-dichlorodiethyl ether with stirring; no sign whatever of reaction was observed. The mixture was heated on a boiling water bath for 10 hr. The reaction mass was subsequently worked up as previously. Fractional distillation gave two fractions: a) 16.2 g of the diisopropyl ester of isopropylphosphinic acid with b.p. 61-63° (1 mm).

Found %: P 14.81; 14.75. $C_9H_{21}O_3P$. Calculated %: P 14.90.

b) 49.5 g (37.8%) of diphosphonate with b.p. 154-155° (0.7 mm).

Found %: P 15.25, 15.31. $C_{16}H_{36}O_7P_2$. Calculated %: P 15.40.

Reaction under the same conditions, with the modification of addition of solution of the phosphite salt in the course of 10 hr to β,β'-dichlorodiethyl ether heated to 100°, raised the yield of diphosphonate to 57.2%. In this case the quantity of low-boiling fraction was considerably smaller.

Bis-(dibutylphosphono)diethyl ether. To 53.4 g of β,β'-dichlorodiethyl ether was added in the course of 6 hr, dropwise with stirring, a freshly prepared solution of the sodium salt of dibutylphosphorous acid (from 17.2 g of sodium and 145 g of dibutyl phosphite) in 400 ml of dry toluene. Heating was continued for 3 hr. Fractionation after the usual working-up gave 8.2 g of the dibutyl ester of butylphosphinic acid (b.p. 147-149° at 9 mm, $n^{20}D$ 1.4295) and 80 g (46.8%) of diphosphonate (b.p. 210-211° at 0.6 mm).

Found %: P 13.62, 13.71. $C_{20}H_{44}O_7P_2$. Calculated %: P 13.52.

Bis-(diethylphosphono)dimethylsulfide. a) To a solution of 14 g of dichlorodimethyl sulfide in 20 ml of dry benzene heated to 80° was added, dropwise with heating in the course of 2.5 hr, a freshly prepared solution of the sodium salt of diethyl phosphite (from 5 g of sodium and 31 g of diethyl phosphite) in 100 ml of dry benzene. After the reaction mass had cooled, a few milliliters of water were added, the precipitate was filtered off, and the filtrate dried over magnesium sulfate before being fractionated in vacuo. There was obtained 6 g of the diethyl ester of ethylphosphinic acid (b.p. 60-61° at 3 mm, $n^{20}D$ 1.4163) and 20 g (57%) of diphosphonate with b.p. 179-180° at 2 mm.

Found %: P 18.37, 18.35; S 9.45, 9.59. $C_{10}H_{24}O_6P_2S$. Calculated %: P 18.54; S 9.58.

b) A mixture of 32 g of triethyl phosphite and 10 g of dichlorodimethyl sulfide was refluxed at 150-170° until ethyl chloride ceased to be liberated (about 16 hr). Fractionation gave 18 g (71%) of the tetraethyl ester of diphosphonodimethyl sulfide, identical with the ester obtained by reaction of dichlorodimethyl sulfide with sodium diethyl phosphite.

Bis-(diisopropylphosphono)dimethyl sulfide. Prepared from 28.2 g of dichlorodimethyl sulfide, 9.9 g of sodium and 71.5 g of diisopropyl phosphite under conditions similar to those for the synthesis of the ethyl analog (except that the salt was added over a period of 10 hr and the reaction mass was washed with water). Yield 51.8 g (61.6%) of diphosphonate; b.p. 164-165° (0.4 mm).

Found %: P. 15.66, 15.70. $C_{14}H_{32}O_6P_2S$. Calculated %: P 15.88.

Bis-(dibutylphosphono)dimethyl sulfide. Prepared from 18.5 g of dichlorodimethyl sulfide, 6.5 g of sodium and 55 g of dibutyl phosphite under conditions similar to those for the synthesis of the isopropyl analog (except that distillation was effected over 3 g of anhydrous potassium carbonate). Yield 32 g (50.8%) of diphosphonate; b.p. 230-232° (2 mm).

Found %: S 7.22, 7.30. $C_{18}H_{40}O_6P_2S$. Calculated %: S 7.17.

Bis-(diisopropylphosphono)diethyl sulfide. To 42.1 g of β,β'-dichlorodiethyl sulfide was added dropwise in the course of 5 hr, with stirring and heating to 106-107° (in a salt bath), the sodium salt of diisopropylphosphorous acid (from 88.5 g of diisopropyl phosphite and 12.3 g of sodium) in 350 ml of dry toluene. Heating and stirring were continued for 5 hr. The product was washed with water, dried and fractionated to give 8 g of the diisopropyl ester of isopropylphosphinic acid and 44 g (39.5%) of diphosphonate; b.p. 150-155° (0.8 mm).

Found %: P 14.95, 15.04. $C_{16}H_{36}O_6P_2S$. Calculated %: P 14.81.

Bis-(dibutylphosphono)diethyl sulfide. Prepared from 21.8 g of β,β'-dichlorodiethyl sulfide, 6.3 g of sodium and 53 g of dibutyl phosphite under conditions similar to those for preparation of the isopropyl analog (except that distillation was effected over 3 g of anhydrous sodium carbonate). Yield 22.8 g (35.2%) of diphosphonate; b.p. 202-204° (0.6 mm).

Found %: S 6.85, 6.92. $C_{20}H_{44}O_6P_2S$. Calculated %: S 6.76.

SUMMARY

Reactions of sodium dialkyl phosphites with dibromo- and dichlorodimethyl ethers, β,β'-dichlorodiethyl ether, dichlorodimethyl and β,β'-dichlorodiethyl sulfides were studied. It was shown that these reactions can lead to satisfactory yields of esters of the corresponding diphosphonic acids.

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REACTION OF SODIUM DIALKYL PHOSPHITES AND SODIUM MONOALKYL PHOSPHONATES WITH ALKYLMAGNESIUM HALIDES

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1964-1968, June, 1960
Original article submitted June 15, 1959

The study of dialkylphosphinic acids of the type of RR'P(O)OH has been neglected, due very largely to the difficulties of their preparation. Of the known methods of synthesis of these compounds, the most interesting is Kosolapoff's method [1] based on Grignard reaction with dialkyl phosphites and subsequent oxidation of the dialkylphosphine oxides [2, 3].

In studying this reaction we were struck by the necessity for use of a large excess of Grignard reagent (3.3 g-atoms of magnesium and 3.5 moles of alkyl halide per mole of dialkyl phosphite). Our investigations showed that dialkyl phosphite decomposes alkylmagnesium halide to the corresponding hydrocarbon.

$$(RO)_2P(O)H + 3R'MgX \rightarrow R_2'POMgX + R'H + 2ROMgX.$$

Butane was isolated, for example, in a yield of about 60%• when diethyl phosphite acted on butylmagnesium bromide under the conditions specified by Kosolapoff.

Wishing to avoid the inefficient consumption of organomagnesium compound, we replaced the dialkyl phosphites by their sodium salts. Reaction with the salts goes without decomposition of the organomagnesium compound and leads to formation of dialkylphosphinic acids with a 30-40% lower consumption of Grignard reagent.

Reaction of alkylmagnesium halides with sodium dialkyl phosphites gives salts of dialkylphosphinous acids.••

$$(RO_2)PONa + 2R'MgX \rightarrow R_2'PONa + 2ROMgX.$$

As was to be expected, these salts similarly to sodium dialkyl phosphites, enter into the reaction, analogous to the Michaelis-Becker reaction.

$$R_2'PONa + RX \rightarrow R_2'P(O)R + NaX$$

Thus, on treatment of the reaction mass, obtained from sodium diethyl phosphite and hexylmagnesium bromide, the oxide of methyl dihexylphosphine separated. Along with this reaction, alkylation of the mixed magnesium alcoholates evidently proceeds.

$$ROMgX + CH_3I \rightarrow ROCH_3 + MgXI$$

Reaction of dialkyl phosphites and their salts with Grignard reagents is a convenient method of synthesis of dialkylphosphinic acids. It is not, however, a general method since it does not enable the preparation of acids with diverse radicals. In the search for more general methods of synthesis of such compounds, a study was made of the reaction of ester-salts of alkylphosphinic acids with alkylmagnesium bromides.

$$R-P(=O)(OR')(ONa) + R''MgBr \xrightarrow{HCl} R''(R)P(=O)-OH + R'OMgBr.$$

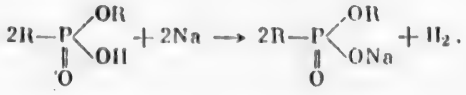
This reaction goes with great difficulty. Prolonged heating of sodium monoethyl methylphosphonate with octylmagnesium bromide gave only an insignificant yield of the dialkylphosphinic acid. Under normal conditions

•The relatively low yield of butane is due to its high solubility in ether, from which it is not easily separated due to the relative closeness of the boiling points.

••Free dialkylphosphinous acids exist in the form of dialkylphosphine oxides R_2PH and are entirely lacking in acid properties [3]. $\begin{matrix} \| \\ O \end{matrix}$

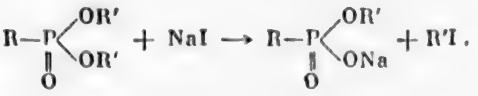
the salt of the isobutyl ester of methylphosphinic acid does not react with octylmagnesium bromide. This type of behavior of esters of acids of pentavalent phosphorus in Grignard reactions has been also observed previously [4].

Ester-salts of alkylphosphinic acids have been obtained by isomerization of sodium dialkyl phosphites under the influence of catalytic quantities of neutral esters of alkylphosphinic acids [5] and by neutralization of monoalkyl phosphonates* by metallic sodium.



It is interesting to note that although monoalkyl phosphonates are strong acids, they do not react with sodium even on prolonged boiling in ethereal solution. Reaction is initiated by addition of catalytic quantities of an alcohol. The acid ester evidently reacts with the alkoxide, the alcohol is regenerated and again reacts with sodium to form alkoxide.

With the objective of preparing ester-salts, we also studied the reaction of alkylation of sodium iodide by neutral esters of alkylphosphinic acids.



Contrary to the findings of V. S. Abramov and E. A. Militskova [6], who claim that "reaction of a sodium halide with esters of alkylphosphinic acids . . . goes only when the radical of the phosphinic acid contains a polar group," it was shown that this reaction also proceeds if the radical does not contain a polar group. As an example, the diethyl ester of methylphosphinic acid smoothly reacts with sodium iodide at 130-160° with formation of ethyl iodide and the sodium salt of ethyl methylphosphinate.

EXPERIMENTAL

Dialkylphosphinic acids. A solution of 2.1 moles of the appropriate Grignard reagent in 800 ml of anhydrous ether was stirred, with cooling, into 1 mole of sodium diethyl phosphite in 600 ml of anhydrous ether at such a rate that the solution boiled gently. For completion of the reaction the mixture was boiled for 2-3 hr and then treated (with cooling) with 200-250 ml of strong hydrochloric acid. The transparent ethereal solution was separated from the precipitate and evaporated until the whole of the solvent had gone off. Into the heated residue was stirred dropwise 75-100 ml of 30% hydrogen peroxide. An exothermic reaction occurred. The resulting dialkylphosphinic acid was purified by crystallization or by distillation in vacuo. The latter method is especially convenient for purification of lower acids which crystallize with difficulty but distil without decomposition. Yield 60-70%.

Properties of the compounds prepared and their analytical data are set forth in the table.

Reaction of sodium salt of dihexylphosphinic acid with methyl iodide. Methyl iodide (0.15 mole) was added to a reaction mass prepared from 0.1 mole of sodium diethyl phosphite and 0.2 mole of hexylmagnesium bromide under the conditions described above. The mixture was stirred at the boil for 3 hr, and then treated with 175 ml of dilute (1 : 10) hydrochloric acid (with cooling). The ethereal layer was washed with 20% alkali solution until it had an alkaline reaction and then with a small quantity of water. After the solvent had been distilled off, the residue was distilled in vacuo to give 9 g of substance with b.p. 180-188° (10 mm), which crystallized on standing. The product was a mixture of dihexyl- and dihexylmethylphosphine oxides. This mixture was dissolved in 50 ml of dry carbon tetrachloride and chlorine was passed through the solution (with cooling) until the latter turned yellow. In this way the dialkylphosphine oxide was converted into dihexylphosphinyl chloride. On the basis of the quantity of chlorine going into reaction (1.4 g), we may conclude that the mixture contained about 50% of secondary phosphine oxide. After the solvent had been distilled off, the residue was stirred (with heating) with 30 ml of saturated potassium carbonate solution. This treatment converted the acid chloride into the salt of dihexylphosphinic acid. The reaction mass was extracted with ether, the solvent was

*A paper on the preparation of monoalkyl phosphonates will shortly be published.

Prep. No.	Formula	Boiling point (pressure in mm)	Melting point *	% P		Equivalent	
				found	calc.	found	calc.
1	$(n.\text{-}C_4H_9)_2P(O)OH$	208–210° (3)	70–71°	17.23	17.39	181.3	178.2
2	$(iso\text{-}C_5H_{11})_2P(O)OH$	230–233 (3)	37–39	14.83	15.02	209.4	206.2
3	$(n.\text{-}C_6H_{13})_2P(O)OH$	--	76–78**	13.01	13.23	238.5	234.2
4	$(n.\text{-}C_7H_{15})_2P(O)OH$	—	74–75**	11.56	11.81	265.2	262.3
5	$(n.\text{-}C_8H_{17})_2P(O)OH$	325–327 (1)	83–84**	10.70	10.67	295.1	290.3

*For substance No. 1 Kosolapoff [1] gives m.p. 71°; Williams [3] gives m.p. 78-79, 77-78, and 85° for substances 3, 4 and 5, respectively.

**From methanol.

driven off from the extract, and the residue distilled in vacuo over a small quantity of anhydrous sodium carbonate. There was obtained 3.8 g (16.5%) of methyldihexylphosphine oxide; b.p. 182-183° (6 mm); m.p. 42-43°. A mixture with the phosphine oxide obtained from hexylmagnesium bromide and the dichloride of methylphosphinic acid melted without depression.

Reaction of sodium monoisobutyl methylphosphonate with octylmagnesium bromide. To 0.1 g-atom of sodium wire in 125 ml of absolute ether was added 0.1 mole of monoisobutyl ester of methylphosphinic acid. The sodium was unchanged after boiling had proceeded for 3 hr. It started to dissolve when 0.5 ml of anhydrous alcohol was added and solution was complete after 5 hr. Into the resulting suspension of sodium salt was stirred 0.12 mole of octylmagnesium bromide. There was no sign of a reaction. The reaction mass was boiled and well stirred for 5 hr, after which it was treated with 50 ml of hydrochloric acid (1 : 2). Three layers formed. The top (ethereal) was combined with the benzene extracts of the middle layer. The solvent was distilled off and the residue fractionated to give 4.8 g (31.6%) of the original monoisobutyl ester of methylphosphinic acid; b.p. 142-144° (1.5 mm); $n^{20}D$ 1.4280.

Found equiv. 155.8. $C_5H_{13}O_3P$. Calculated equiv. 152.1.

A fraction corresponding to methyloctylphosphonic acid was absent.

Reaction of sodium iodide with diethyl methylphosphonate. A mixture of 30.4 g of diethyl methylphosphonate and 30 g of pulverized, dry sodium iodide was heated with periodic shaking in a flask arranged for distillation. Distillation of ethyl iodide commenced at 130°; 27.2 g (87%) of the iodide had come over after 3 hr heating at 130-160°; b.p. 71-73°, d^{20}_4 1.9324. Traces of alkyl halide were eliminated from the reaction mass by heating in vacuo. There was obtained 28.7 g (98%) of the sodium salt of the ethyl ester of methylphosphinic acid in the form of a white, hygroscopic powder.

Found %: P 21.03. $C_3H_8O_3PNa$. Calculated %: P 21.21.

Reaction of sodium monoethyl methylphosphonate with octylmagnesium bromide. To 0.12 mole of octylmagnesium bromide in 100 ml of ether was added (with stirring) 0.1 mole of sodium monoethyl methylphosphonate. No reaction was observed. The mixture was boiled for 16 hr and then treated as described above. Fractionation gave 18.7% of methyloctylphosphinic acid with b.p. 220-225° (3 mm).

Found %: P 15.80. Equiv. 195.4. $C_9H_{21}O_2P$. Calculated %: P 16.1. Equiv. 192.1.

SUMMARY

1. It was shown that sodium dialkyl phosphites easily react with alkylmagnesium halides to form salts of dialkylphosphinic acids; alkylation with alkyl halides converts the products into phosphine oxides, while oxidation gives dialkylphosphinic acids.

2. It was found that salts of esters of alkylphosphinic acids enter with great difficulty into the Grignard reaction.

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ESTERIFICATION OF BIS(HYDROXYMETHYL)TETRAMETHYLDISILOXANE BY ACID CHLORIDES

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1968-1971, June, 1960
Original article submitted June 23, 1959

It has been reported that bis(hydroxymethyl)tetramethyldisiloxane easily (even on standing) condenses with release of water and increase in viscosity [1]. This behavior was attributed to the instability of the substance. It was of definite interest to study the properties of bis(hydroxymethyl)tetramethyldisiloxane and to clarify the possibility of preparing its esters by normal esterification methods.

In the present work the stability of bis (hydroxymethyl)tetramethyldisiloxane was investigated and its reactions with methacrylyl chloride and allyl chloroformate were studied. The stability was studied by varying the conditions of its synthesis. Bis(acetoxymethyl)tetramethyldisiloxane was treated with methanol in presence of hydrogen chloride, the reaction mixture was held at about 20° for 72 hr, and the methanol and resulting methyl acetate distilled off from the acidic reaction mixture (or after neutralization of the latter by sodium bicarbonate). It was found that bis(hydroxymethyl)tetramethyldisiloxane, when obtained from the reaction mixture neutralized before distillation of the methanol, contained 15.38% of hydroxyl groups and 28.32% of silicon, while the product obtained after distillation of the methanol from the acid reaction mixture contained 16.32% of hydroxyl groups and 28.19% of silicon (calculated values are 17.5% of hydroxyl groups and 28.86% of silicon). These experiments showed that heating of bis(hydroxymethyl)tetramethyldisiloxane in neutral or acidic media (under the conditions of its synthesis) does not lead to a lower content of hydroxyl groups. Fractionation of the crude product gave a fraction boiling at 118-119° (7 mm) containing 16.97% of hydroxyl groups and 28.17% of silicon. Analysis of the fraction corresponded to bis(hydroxymethyl)tetramethyldisiloxane. No increase in viscosity or separation of water was observed after keeping of both the distilled and the undistilled bis-(hydroxymethyl)tetramethyldisiloxane for 4 months at room temperature. These data demonstrate the adequate stability of bis(hydroxymethyl)tetramethyldisiloxane after neutralization of the crude product by sodium bicarbonate.

Esterification was carried out with methacrylyl chloride and allyl chloroformate. Study of the esterification with the second compound showed that reaction goes according to the equation

$$HOCH_2Si(CH_3)_2OSi(CH_3)_2CH_2OH + 2CH_2{=}CHCH_2OCOCl \xrightarrow{-2HCl}$$

$$\rightarrow CH_2{=}CHCH_2OCOOCH_2Si(CH_3)_2OSi(CH_3)_2CH_2OCOCH_2CH{=}CH_2$$

Bis(carboxyallylatomethyl)tetramethyldisiloxane was isolated in a yield of 30%.

Formula	Boiling point (at 2 mm)	d_4^{20}	n_D^{20}	MR found	MR calc.	Bromine no. found	Bromine no. calc.
$(CH_2{=}CHCH_2OCOOCH_2Si(CH_3)_2)_2O$	147–148°	1.0400	1.4406	91.83	92.06	89.2	89.3
$CH_2{=}C(CH_3)COOCH_2Si(CH_3)_2OSi(CH_3)_2CH_2OCOCH{=}CH_2$	138–139	1.0202	1.4428	89.89	90.33	90.3	90.4

Reaction of bis(hydroxymethyl)tetramethyldisiloxane with a mixture of allyl chloroformate and methacrylyl chloride led to formation of a full ester—1-methacrylatomethyl-2-carboxyallylatomethyltetramethyldisiloxane—in a yield of 19%.

$$HOCH_2Si(CH_3)_2OSi(CH_3)_2CH_2OH + CH_2{=}CHCH_2OCOCl + CH_2{=}C(CH_3)COCl \xrightarrow{-2HCl}$$

$$\rightarrow CH_2{=}CHCH_2OCOOCH_2Si(CH_3)_2OSi(CH_3)_2CH_2OCOC(CH_3){=}CH_2$$

The poor yield of these esters is due to the difficulty of separating them because of formation of partial esterification products and of the great susceptibility to polymerization.

In the table are set forth the properties of the synthesized esters. The products polymerize easily in presence of peroxide initiators with formation of solid, vitreous polymers.

EXPERIMENTAL

1. Preparation of bis(hydroxymethyl)tetramethyldisiloxane. A solution of 278 g of bis(acetoxymethyl)-tetramethyldisiloxane ($n^{20}D$ 1.4260, d^{20}_{20} 1.0073, acetyl number 41.6) in 750 ml of anhydrous methanol containing 3 wt.-% HCl was placed in a flask of 1.5 liters capacity and held at 20° for three days. The methanol and the resulting methyl acetate were then distilled off from a Favorskii flask on a water bath. Distillation was effected at atmospheric pressure from nonneutralized and from previously neutralized mixture. In each case, after completion of distillation traces of methanol were eliminated by holding the product in vacuo (15 mm) for 3 hr. The purity of the product was checked by Verley determinations of hydroxyl groups [2]. Yield 188 g (97%). Part of the crude product was subjected to vacuum fractionation. A fraction boiling at 118-119° (7 mm) was obtained.

$n^{20}D$ 1.4374, d^{20}_4 0.9858, MR 51.56; calc. 51.52.

Found %: C 36.95; H 9.33; Si 28.17; OH 16.97. $C_6H_{18}O_3Si_2$. Calculated %: C 37.12; H 9.27; Si 28.86; OH 17.82.

2. Preparation of bis(carboxyallylatomethyl)tetramethyldisiloxane. A three-necked, 0.5-liter flask, fitted with mechanical stirrer, thermometer and dropping funnel, was charged with 75 ml of pyridine and cooled to −10°. To the cooled pyridine, in the course of 30 min at −5 to −10°, was added dropwise 0.25 mole of bis(hydroxymethyl)tetramethyldisiloxane (containing 15.3% of OH groups); the solution was then again cooled to −10° and 0.62 mole of allyl chloroformate was added dropwise at such a rate that the temperature of the reaction mixture did not rise above 0° (about 2 hr). The mixture was then stirred at 20° for an hour, after which it was again cooled

to −10°. This was followed by addition of 100 ml of HCl solution (1 : 1) at below 0°. The resulting layer of ester was separated. The product was dissolved in an equal volume of ether, washed with dilute hydrochloric acid and then with water until neutral, and dried over Na_2SO_4. The ethyl ether was driven off and the residue fractionated. The bis(carboxyallylatomethyl)tetramethyldisiloxane fraction came over at 146-148° (2 mm). Yield 30%.

Found %: C 45.98; H 7.74; Si 15.25. $C_{14}H_{26}O_7Si_2$. Calculated %: C 46.10; H 7.18; Si 15.47.

3. Preparation of 1-methacrylatomethyl-2-carboxyallylatomethyltetramethyldisiloxane. A mixture of 0.31 mole of allyl chloroformate and 0.31 mole of methacrylyl chloride was added dropwise to a solution of 0.3 mole of bis(hydroxymethyl)tetramethyldisiloxane in excess of pyridine under the conditions of the preceding preparation. Fractional distillation gave a fraction with b.p. 137-140° (2 mm). Yield 19%.

Found %: C 48.95; H 7.97; Si 16.15. $C_{14}H_{26}O_6Si_2$. Calculated %: C 48.55; H 7.51; Si 16.19.

SUMMARY

1. Bis(hydroxymethyl)tetramethyldisiloxane was prepared in 97% yield. It has satisfactory stability.

2. Reaction of methacrylyl chloride and allyl chloroformate with bis(hydroxymethyl)tetramethyldisiloxane gave the esters: 1-methacrylatomethyl-2-carboxyallylatomethyldisiloxane and bis(carboxyallylatomethyl)tetramethyldisiloxane.

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CHLORIDES OF N-ARYLSULFONYL-ARENEIMINOSULFONIC ACIDS

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1971-1975,
June, 1960
Original article submitted June 26, 1959

The recently prepared acid chlorides of N-dichlorophosphinyl-areneiminosulfonic acids [1] are N-substituted acid chlorides of areneiminosulfonic acids as well as N-substituted dichlorides of amidophosphoric acid. Therefore they combine the properties of chlorides of iminosulfonic acids and of dichlorides of amidophosphoric acids. In order to study the properties of chlorides of iminosulfonic acids lacking in the properties of chlorides of acids of the other type, it would be necessary to prepare derivatives of chlorides of iminosulfonic acids containing at the nitrogen atom a substituent devoid of active chlorine atoms. For this purpose, chlorides of N-arylsulfonyl-areneiminosulfonic acids were synthesized by the action of sodium salts of chloroamides of arenesulfonic acids on chlorides of arenesulfinic acids according to the equation

$$ArSOCl + NaClNSO_2Ar' \longrightarrow NaCl + ArSO(=NSO_2Ar')Cl.$$

Chlorides of N-arylsulfonyl-areneiminosulfonic acids (Table 1) are colorless, crystalline, low-melting substances, insoluble in water, and possessing a weak odor reminiscent of chlorides of arenesulfonic acids.

In their chemical properties, chlorides of N-arylsulfonyl-areneiminosulfonic acids are typical acid chlorides; they react with facility with substances containing active atoms of hydrogen or metals with formation of the corresponding derivatives of N-arylsulfonyl-areneiminosulfonic acids.

At room temperature, chlorides of N-arylsulfonyl-areneiminosulfonic acids are hydrolyzed very slowly by water, due to their poor solubility in water. Boiling with water (heterogeneous conditions) results in very much faster hydrolysis, the rate following a zero order equation (Fig. 1), which is likewise accounted for by the poor solubility of the acid chlorides in water (constant concentration of the saturated aqueous solution so long as there are two phases).

Treatment of chlorides of N-arylsulfonyl-areneiminosulfonic acids with caustic alkalies in aqueous alcoholic solutions converts them in good yields into the alkali salts of the corresponding diarylsulfonylimides, which on acidification give the free diaryldisulfonylimides (Table 2) according to the equation

$$ArSO(=NSO_2Ar)Cl \xrightarrow{+2NaOH} (ArSO_2NSO_2Ar)Na \xrightarrow{+H^+} ArSO_2NHSO_2Ar.$$

This reaction, in line with the analytical data, affords full and strict confirmation of the structure of acid chlorides of N-arylsulfonyl-areneiminosulfonic acids.

Acid chlorides of N-arylsulfonyl-areneiminosulfonic acids are likewise hydrolyzed in acid solutions to diaryldisulfonylimides, but the hydrolysis in part goes further with formation of amides of sulfonic acids.

$$ArSO(=NSO_2Ar)Cl \xrightarrow{+H_2O} ArSO_2NHSO_2Ar \xrightarrow{+2H_2O} 2ArSO_2NH_2.$$

Under mild conditions the yield of diaryldisulfonylimides in acid hydrolysis is about 80%; that of amides of sulfonic acids about 10%.

TABLE 1

Chlorides of N-Arylsulfonyl-areneiminosulfonic Acids of the Type of ArSO(= NSO_2Ar')Cl

Ar	Ar'	Yield (%)	Melting point	Outward appearance; crystallization medium	Formula	Found (%)		Calc. (%)		Solubility *				
						Cl	S	Cl	S	ether	C_6H_6	n-hexane	ligroine **	chloroform
C_6H_5	C_6H_5	57	93—94°	Prisms; benzene; n-hexane	$C_{12}H_{10}O_3NS_2Cl$	—	20.68, 20.54	—	20.28	+	+	+	+	+
C_6H_5	p-$CH_3C_6H_4$	76	73—74	Prisms; ether	$C_{13}H_{12}O_3NS_2Cl$	10.88, 10.98	19.97, 20.01	10.77	19.42	+	+	—	—	+
C_6H_5	p-$CH_3OC_6H_4$	93	76—78	Prisms, ether, alcohol	$C_{13}H_{12}O_4NS_2Cl$	10.29, 10.33	18.43, 18.30	10.28	18.52	+	+	—	—	+
C_6H_5	p-ClC_6H_4	55	110—111	Needles; CCl_4, alcohol	$C_{12}H_9O_3NS_2Cl_2$	20.42, 20.32	—	20.29	18.29	+	+	—	—	+
C_6H_5	p-$NO_2C_6H_4$	73	129—130	The same	$C_{12}H_9O_5N_2S_2Cl$	9.89, 9.98	18.31, 18.20	9.85	17.75	—	+	—	=	+
C_6H_5	β-$C_{10}H_7$	51	89—91	Prisms; CCl_4, alcohol	$C_{16}H_{12}O_3NS_2Cl$	9.86, 9.77	17.51, 17.44	9.71	17.53	+	+	—	—	+
p-$CH_3C_6H_4$	C_6H_5	65	94—95	The same	$C_{13}H_{12}O_3NS_2Cl$	11.01, 11.12	19.98, 19.49	10.77	19.42	—	+	—	—	+
p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	78	76—78	The same	$C_{14}H_{14}O_3NS_2Cl$	10.19, 10.23	19.31, 19.18	10.33	18.63	+	+	—	—	+
p-$CH_3C_6H_4$	p-$CH_3OC_6H_4$	91	121—122	Prisms; CCl_4, CH_2Cl_2	$C_{14}H_{14}O_4NS_2Cl$	10.15, 10.16	17.64, 17.47	9.87	17.80	—	+	—	—	+
p-$CH_3C_6H_4$	p-ClC_6H_4	98	89—90	Needles; CCl_4, alcohol	$C_{13}H_{11}O_3NS_2Cl_2$	19.99, 19.84	17.84, 17.95	19.51	17.99	—	+	+	—	+
p-$CH_3C_6H_4$	p-$NO_2C_6H_4$	73	138—139	alcohol	$C_{13}H_{11}O_5N_2S_2Cl$	10.10, 10.14	17.11, 17.06	9.48	17.09	—	+	—	—	+
p-$CH_3C_6H_4$	β-$C_{10}H_7$	63	113—115	Plates; alcohol	$C_{17}H_{14}O_3NS_2Cl$	9.39, 9.23	16.88, 17.15	9.35	16.86	—	+	—	=	+

* ‡ easily soluble at 20°; + easily soluble at the boil; —sparingly soluble at the boil; = insoluble at the boiling point.

All of the substances are readily soluble at 20° in acetone, readily soluble at the boil in carbon tetrachloride, methanol and ethanol, insoluble in water.

** B.p. 50-60°.

TABLE 2

Diarylsulfonylimides of the Type of $ArSO_2NHSO_2Ar'$

Ar	Ar'	Melting point	Outward appearance; crystallization medium	Formula	Found (%)	Calc. (%)	Solubility*			
							water	ether	benzene	CCl_4
C_6H_5 [2]	C_6H_5	157–158° **	Prisms, benzene	—	****	—	+	+ +	+	—
C_6H_5 [2]	p-$CH_3C_6H_4$	169–171 ***	The same	—	****	—	+	—	—	=
C_6H_5	p-$CH_3OC_6H_4$	149–151	The same	$C_{13}H_{13}O_5NS_2$	S 19.68, 19.58	S 19.57	+	—	—	=
C_6H_5 [3]	p-ClC_6H_4	177–179 *****	Needles; alcohol	$C_{12}H_{10}O_4NS_2Cl$	S 19.63, 19.58	S 19.31	+	—	+	=
C_6H_5	p-$NO_2C_6H_4$	168–170	The same	$C_{12}H_{10}O_6N_2S_2$	N 8.11, 8.25	N 8.19	+ +	+	+	=
C_6H_5	β-$C_{10}H_7$	143–145	Prisms; alcohol	$C_{16}H_{13}O_4NS_2$	S 18.51, 18.64	S 18.44	+	+ +	+	=
p-$CH_3C_6H_4$ [4,5]	p-$CH_3C_6H_4$	171–173******	Plates; benzene	—	—	—	+	+ +	+	—
p-$CH_3C_6H_4$	p-$CH_3OC_6H_4$	153–154	Prisms; benzene	$C_{14}H_{15}O_5NS_2$	S 18.60, 18.76	S 18.77	+	—	+	=
p-$CH_3C_6H_4$ [6]	p-ClC_6H_4	161–163*****	Plates; alcohol	$C_{13}H_{12}O_4NS_2Cl$	S 18.87, 18.72	S 18.52	+	+ +	+	—
p-$CH_3C_6H_4$ [7]	p-$NO_2C_6H_4$	198–200*****	Prisms; alcohol	$C_{13}H_{12}O_6N_2S_2$	N 7.96, 8.08	N 7.87	+	—	—	=
p-$CH_3C_6H_4$	β-$C_{10}H_7$	142–144	Plates; alcohol	$C_{17}H_{15}O_4NS_2$	S 17.38, 17.42	S 17.73	+	+	+	=

*See Table 1 for symbols. All of the substances are readily soluble at 20° in alcohol and acetone, insoluble in boiling ligroine.

**Agrees with literature data.

***According to [2] m.p. 164-166°.

****Identified by mixed melting test.

*****Melting points not reported in [3], [6], and [7].

******According to [4] m.p. 174 and 169°; melting point not given in [5].

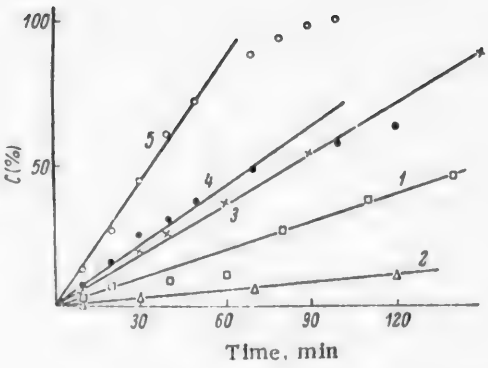

Fig. 1. Hydrolysis of $C_6H_5SO(=NSO_2Ar)Cl$ by boiling water. Numbers of curves refer to composition of Ar: 1) C_6H_5, 2) p-$CH_3C_6H_4$, 3) p-$CH_3OC_6H_4$, 4) p-ClC_6H_4, 5) p-$NO_2C_6H_4$.

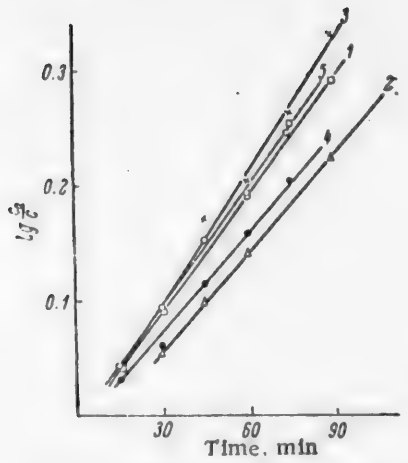

Fig. 2. Hydrolysis of $C_6H_5SO(=NSO_2Ar)Cl$ in 0.0005 molar aqueous acetone (1 : 1) solution at 50°. See Fig. 1 for key to numbers on curves.

TABLE 3

Hydrolysis of Chlorides of N-Arylsulfonylbenzeneiminosulfonic Acids of the Type of $C_6H_5SO(=NSO_2Ar)Cl$

Ar	$K \cdot 10^4$/min
C_6H_5	8.1
p-$CH_3C_6H_4$	7.5
p-$CH_3OC_6H_4$	10.0
p-ClC_6H_4	8.4
p-$NO_2C_6H_4$	8.7
$C_6H_5SO_2Cl$	92.0*

In 0.0005 M aqueous acetone solution (1 : 1) at 50°, the velocity constants of hydrolysis of acid chlorides of N-arylsulfonyl-areneiminosulfonic acids are approximately ten times smaller than the velocity constants of hydrolysis of the chloride of benzenesulfonic acid (Table 3). Hydrolysis follows a first-order equation (Fig. 2). Substituents in the aromatic nucleus of the N-arylsulfonyl group have no appreciable influence on the rate of hydrolysis (Table 3).

Unlike acid chlorides of arenesulfonic acids, chlorides of N-arylsulfonyl-areneiminosulfonic acids react very slowly with alcohols; after short-period boiling they can be recrystallized substantially unchanged from 96% alcohol.

EXPERIMENTAL

Chlorides of N-arylsulfonyl-areneiminosulfonic acids (Table 1). In small portions 0.05 mole of finely pulverized, anhydrous sodium salt of the chloroamide of the arenesulfonic acid was slowly stirred into a solution of 0.05 mole of the chloride of the arenesulfinic acid in 80 ml of benzene. Slight heat was generated. The reaction mixture was refluxed for 1-1.5 hr on a water bath. The sodium chloride was suction-filtered and the benzene distilled in vacuo on a water bath. The residue contained the acid chloride of the N-arylsulfonyl-areneiminosulfonic acid in the form of an oil which crystallized on cooling. Purification was effected by recrystallization from a suitable solvent. The chlorides of benzene- and toluenesulfinic acids were prepared by the literature methods [9]. Sodium salts of chloroamides of arenesulfonic acids were dried as described previously [10].

Hydrolysis of chlorides of N-arylsulfonyl-areneiminosulfonic acids. A. Hydrolysis with boiling water (Fig. 1). A mixture of 0.002 mole of acid chloride and 20 ml of water was refluxed and quickly cooled. The resulting acid was titrated with alkali in presence of phenolphthalein.

B. Hydrolysis in aqueous alcoholic alkali solutions (Table 2). To a solution of 0.002 mole of chloride of N-arylsulfonyl-areneiminosulfonic acid in 10 ml of methanol was added a solution of 0.004 mole of sodium hydroxide in 0.5 ml of water. The mixture was boiled for 15 min and then evaporated to dryness in vacuo. The residue was dissolved in the minimum quantity of water, and the solution filtered and acidified with hydrochloric acid. The diaryldisulfonylimide came down and was suction-filtered, dried, and purified by crystallization. Yields 80-90%.

*The literature gives for $C_6H_5SO_2Cl$ under the same conditions $k = 115 \times 10^{-3}$/min [8].

C. Hydrolysis in aqueous-alcoholic solutions of acids. A mixture of 0.005 mole of chloride of N-arylsulfonyl-areneiminosulfonic acid, 20 ml of ethanol and 20 ml of 1 N hydrochloric acid was boiled until a transparent solution had been formed (about 1.5 hr). The solution was then evaporated in vacuo until crystals of diaryldisulfonylimide came down. After cooling, the precipitate was suction-filtered and washed with a small quantity of water. Yield about 80%. The filtrate was evaporated to dryness and the residue treated with sodium bicarbonate solution. The arenesulfonamide remained undissolved and was suction-filtered and washed with water. Yield about 10%; identification by mixed melting point test.

D. Hydrolysis in aqueous acetonic solutions (Fig. 2, Table 3). A 0.005 molar solution of the acid chloride in aqueous acetone (1 : 1) was placed in a water thermostat heated to 50 ± 0.01°. Titration was performed with 0.01 N sodium hydroxide solution in presence of Bromophenol Blue by the method of withdrawal of samples.

SUMMARY

Acid chlorides of N-arylsulfonyl-areneiminosulfonic acids were prepared by the action of acid chlorides of arenesulfinic acids on sodium salts of chloroamides of arenesulfonic acids. Their hydrolysis was studied.

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ALKYLATION OF PHOSPHORUS DIIODIDE

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1976-1981, June, 1960
Original article submitted June 26, 1959

Addition of alkyl halides to halogenated derivatives of trivalent phosphorus is of theoretical and practical interest, but has been little studied.

Auger [1] reported that halogenated compounds of phosphorus, in particular phosphorus diiodide, combine with alkyl halides on heating with formation of a mixture of quaternary phosphonium compounds (RPX_4, R_2PX_3, R_3PX_2), which after hydrolysis give a mixture of alkylphosphinic acids, dialkylphosphinic acids and trialkylphosphine oxides. The paper does not describe experiments, does not present analytical data and does not describe the properties of the compounds obtained; it is merely indicated that the reaction products are obtained in poor yields. Clay [2] showed that in presence of an equivalent quantity of aluminum chloride, alkyl halides easily enter into reaction with phosphorus trichloride with formation of complexes $-(RPCl_3)^+AlCl_4^-$ – which react with water to give chlorides of alkylphosphinic acids.

The literature accordingly does not contain any specific and reliable data for the reaction of halogen compounds of trivalent phosphorus with alkyl halides as such (in Clay's reaction phosphorus trichloride reacts not with alkyl halides, but with their highly active complexes with aluminum chloride).

Detailed investigations by A. E. Arbuzov's school [3] and by many other workers [4, 5] showed that addition of electrophilic reagents, including alkyl halides, to compounds of trivalent phosphorus proceeds the more easily the more nucleophilic is the phosphorus component and the more electrophilic is the added component. It can therefore be confidently asserted that alkyl halides will combine with the greatest facility of all with the most nucleophilic halogen compounds of trivalent phosphorus, namely phosphorus triiodide and diiodide.

Convenient methods were recently developed for preparation of phosphorus tri- and diiodides [6], and so it has become possible to make a close study of their chemical properties.

The objective of the present work was clarification of the possibility of alkylation of phosphorus tri- and diiodides by alkyl halides (benzyl iodide and the simplest alkyl iodides).

When a mixture of phosphorus diiodide and benzyl iodide is heated, an exothermic reaction starts at 110-115° and leads to formation of a compound that hydrolyzes to tribenzylphosphine oxide (Expt. 1). The yield of tribenzylphosphine oxide (95%) and the quantity of iodine separated on hydrolysis show that the reaction goes by the following mechanism:

$$P_2I_4 + 6C_6H_5CH_2I \longrightarrow \left\{ \begin{array}{l} (C_6H_5CH_2)_6P_2I_x \cdot I_{10-x} \\ \text{or} \\ 2(C_6H_5CH_2)_3PI_x \cdot I_{5-x} \end{array} \right. \xrightarrow[\text{or } OH^-]{+SO_2,\ +H_2O} 2(C_6H_5CH_2)_3PO.$$

The intermediate complex easily splits off iodine under the action of caustic alkali or reducing agents, but does not split it off on gentle heating in vacuo. Reaction between phosphorus diiodide and benzyl iodide can also be effected in a solvent. The most suitable solvent for this purpose is chlorobenzene (Expt. 2).

A secondary product, formed in small quantity during reaction of benzyl iodide with phosphorus diiodide, is a compound which hydrolyzes to dibenzylphosphinic acid.

Phosphorus diiodide also reacts with benzyl chloride. In this case, however, the yields of tribenzylphosphine oxide are rather lower. Phosphorus trichloride is a secondary product (Expt. 3).

It was previously established that phosphorus diiodide is formed from iodine and red phosphorus at a temperature of about 180° [6]. Hence for the synthesis of trialkylphosphine oxides there is no need to start from phosphorus diiodide itself. Instead equivalent quantities of iodine and red phosphorus can be successfully used (Expt. 4). An excess of red phosphorus and iodine must be taken in order to obtain good yields of tribenzylphosphine oxide (87%) when benzyl chloride is used (Expt. 5).

Iodine is released when phosphorus diiodide reacts with benzyl iodide, and phosphorus diiodide can be formed by reaction of iodine with red phosphorus during the reaction. Addition of iodine to the reaction mixture is therefore unnecessary for preparation of trialkylphosphine oxides from alkyl iodides. One can start from alkyl iodides and red phosphorus and only add iodine and phosphorus diiodide in catalytic quantities in order to initiate the reaction. Experimental data fully confirmed these ideas (Expt. 6). Direct alkylation of phosphorus is thus effected formally and practically.

Trivalent phosphorus also enters into reaction with benzyl iodide, but the yields of tribenzylphosphine oxide and dibenzylphosphinic acid are very much lower. The main bulk of reaction product, after hydrolysis, is a viscous resin (Expt. 7). In this case alkylation evidently goes only at the expense of the phosphorus diiodide, which is formed during the reaction in accordance with the equation

$$2PI_3 \rightarrow I_2 + P_2I_4.$$

This hypothesis is consistent with the fact that the reaction goes in the usual manner with good yields (Expt. 8) if red phosphorus is added to the reaction mixture in the quantity needed for formation of phosphorus diiodide.

p-Chlorobenzyl iodide reacts with phosphorus diiodide in the same manner as benzyl iodide. p-Nitrobenzyl iodide reacts very vigorously with formation of resinous products.

It is not possible to steer the reaction of phosphorus diiodide with benzyl iodide to give mono- and dibenzylphosphinic acids as the main reaction products. This is because the partially alkylated product undergoes further alkylation by benzyl iodide very much more quickly than the phosphorus diiodide (cf. [7]), since the products of partial alkylation of phosphorus diiodide are undoubtedly more active nucleophilic reagents than phosphorus diiodide itself (cf. [5]).

Alkyl iodides react with phosphorus diiodide in similar fashion to give benzyl iodide, but the reaction goes with less facility (only on heating for several hours in sealed tubes at 200°). Hydrolysis of the initial reaction products gives trialkylphosphine oxides whose properties correspond to those described in the literature. The table shows yields of trialkylphosphine oxides obtained by the action of methyl, n-propyl, n-butyl and isoamyl oxides on phosphorus diiodide, the period of heating of the reaction mixture, and methods of isolation of the reaction products.

If the reaction is performed in an autoclave with an efficient stirrer, the phosphorus diiodide may be replaced by a mixture of red phosphorus with a small quantity of iodine. Reaction starts at 200-220° and is exothermic (the temperature rises by 10° and there is a sharp increase in pressure).

Reaction of red phosphorus with benzyl iodide and alkyl iodides in presence of catalytic quantities of phosphorus diiodide or iodine can thus be regarded formally as direct alkylation of phosphorus. In reality, however, the process undoubtedly involves intermediate formation of phosphorus diiodide.

As far back as 1871, Crafts and Silva [13] suggested that phosphorus triiodide is formed as intermediate product when yellow phosphorus is alkylated by alkyl iodides. Masson and Kirkland [14] disagreed with this conclusion and assumed that alkyl iodides directly alkylate phosphorus. The experiments described above show that phosphorus diiodide is actually the intermediate product, and it is very unlikely that phosphorus could directly combine with alkyl halides.

Reaction of Alkyl Iodides with Phosphorus Diiodide in Sealed Tubes

Alkyl	Duration of heating (hr)	Yield* (%)	Method of isolation**	Constants and literature citations
CH_3	4	75	A	M.p. 140—141° [8]
C_2H_5	6	70	A	b.p. 240° [9], 84—85° (3mm)
n -C_3H_7	4	25	A	B.p. 260—265°; M.p. 38° [10]
n -C_4H_9	8	75	B	B.p. 300° [11]; M.p. 53—54°
iso -C_5H_{11}	1.5	69	B	M.p. 60—65 [12]; B.p. 325—330°

In the experiments of Emeleus and Smith and those of Bennett, Emeleus and Haszeldine [15] on alkylation of phosphorus with trifluoromethane and heptafluoropropane, the intermediate product of reaction is also, in all probability, phosphorus diiodide.

EXPERIMENTAL

Reaction of phosphorus diiodide with benzyl iodide and benzyl chloride. Expt. 1. A mixture of 0.06 mole of benzyl iodide and 0.01 mole of phosphorus diiodide was slowly heated on an oil bath. At 110° (temperature of the reaction mixture) a violent exothermic reaction commenced, the temperature rising to 170° before falling to 120° (at a bath temperature of 110°). This temperature was maintained for another 20 min. The reaction mixture was then a dark, viscous mass which solidified on cooling. It was treated with sodium sulfite solution (or 2 N sodium hydroxide solution) with gentle heating. The resulting precipitate of tribenzylphosphine oxide was suction-filtered and thoroughly washed with water; yield 95%; m.p. 206-208°. After crystallization from alcohol the m.p. rose to 212-213° in agreement with the literature [16].

Expt. 2. A mixture of 0.06 mole of benzyl iodide, 0.01 mole of phosphorus diiodide and 50 ml of chlorobenzene was boiled for 2 hr. It was then transferred to a separating funnel and vigorously shaken with an aqueous solution of sodium sulfite until completely decolorized. If tribenzylphosphine oxide came out of solution, chlorobenzene was added until the precipitate dissolved completely. The chlorobenzene layer separated and dried with sodium sulfate, and the chlorobenzene was distilled in vacuo to leave a residue of tribenzylphosphine oxide; yield 92%. The aqueous layer was acidified; dibenzylphosphinic acid came down in a yield of 3%; m.p. 189-190° in agreement with the literature [16].

Expt. 3. A mixture of 0.01 mole of phosphorus diiodide and 0.06 mole of benzyl chloride was heated until an exothermic reaction commenced (at about 150°) and held at the same temperature for 30 min. During the reaction 0.4 g of phosphorus trichloride distilled over (0.003 mole). The reaction mixture was treated hot with sodium sulfite solution. The precipitated tribenzylphosphine oxide was suction-filtered and washed with water; yield 62%. Dibenzylphosphinic acid was precipitated from the solution with hydrochloric acid; yield 21%.

Expt. 4. A mixture of 0.01 g-atom of red phosphorus, 0.02 g-atom of iodine and 0.03 mole of benzyl iodide was heated on an oil bath as in Expt. 1. Yield of tribenzylphosphine oxide 81%; that of dibenzylphosphinic acid 7%.

Expt. 5. Reactants employed, under the conditions of Expt. 4, were 0.16 g-atom of red phosphorus, 0.3 g-atom of iodine and 0.3 mole of benzyl chloride. Yield of tribenzylphosphine oxide 87%, of dibenzylphosphinic acid 5%.

Expt. 6. Under the same conditions 0.06 mole of benzyl iodide, 0.03 g-atom of red phosphorus and 0.001 mole of phosphorus diiodide gave 92% of tribenzylphosphine oxide and 2% of dibenzylphosphinic acid.

*Yields are those of crude products.

**See Experimental.

Expt. 7. A mixture of 0.01 mole of phosphorus triiodide and 0.03 mole of benzyl iodide was slowly heated on a water bath. An exothermic reaction started at 150° and the temperature rose to 170°. After cooling of the mass to 120°, this temperature was maintained for 30 min and then the reaction mixture was treated with aqueous sodium sulfite solution. A brown, semisolid oil was obtained from which, after crystallization from alcohol, was isolated 22% of tribenzylphosphine oxide and 16% of dibenzylphosphinic acid.

Expt. 8. Reaction between 0.01 mole of phosphorus triiodide, 0.01 g-atom of red phosphorus and 0.6 mole of benzyl iodide was performed in the usual manner. Yield of tribenzylphosphine oxide 89%, of dibenzylphosphinic acid 3%.

Tri-p-chlorotribenzylphosphine oxide. A mixture of 0.01 mole of phosphorus diiodide and 0.06 mole of p-chlorobenzyliodide was heated on an oil bath until an exothermic reaction started (120°). Heating at 120° was continued for another 30 min. The reaction mixture was treated as in preceding experiments. The insoluble product was a mixture of tri-p-chlorotribenzylphosphine oxide and unreacted p-chlorobenzyl iodide which was easily washed out with ether. Yield of tri-p-chlorotribenzylphosphine oxide 50%. Crystallization from alcohol gave stout, colorless needles with m.p. 183-184°. Insoluble in water and ether, highly soluble in methanol and chloroform, crystallizing from ethanol, benzene and carbon tetrachloride.

Found %: Cl 25.12, 25.08. $C_{21}H_{18}OPCl_3$. Calculated %: Cl 25.14.

Reaction of phosphorus diiodide with alkyl iodides. A mixture of phosphorus diiodide and alkyl iodide in 1:6 molar ratio was heated for several hours in sealed tubes at 200°. Reaction products were isolated by two methods.

A. The reaction mixture was treated with concentrated nitric acid until iodine ceased to separate out, the iodine was filtered off and the solution evaporated nearly to dryness. The residue was neutralized with sodium carbonate solution, again evaporated to dryness and treated with a small quantity of alcohol. The insoluble salts were filtered off and the alcohol distilled off; the residue contained trialkylphosphine oxide. Trimethylphosphine oxide was purified by sublimation; triethylphosphine and triisopropylphosphine oxides were distilled.

B. The reaction mixture was gently heated with sodium sulfite solution. The resulting trialkylphosphine oxide was extracted with ether, the ether was driven off and the trialkylphosphine oxide distilled.

Reaction of alkyl iodides with red phosphorus in presence of iodine. A mixture of 3 moles of alkyl iodide, 1.5 moles of red phosphorus and 0.01 g-atom of iodine was slowly heated in a steel autoclave fitted with an efficient stirrer. An exothermic reaction commenced at 200-220° and was marked by a sharp jump in pressure. In the case of butyl iodide the pressure rose from 20 to 35 atm in 3-4 min. Heating of the autoclave was stopped as soon as the exothermic reaction started, but the temperature continued to rise at the expense of the reaction heat (usually by 10-15°). After a few minutes, the pressure gradually started to fall and fell to 15 atm in 30 min. The reaction mixture, after cooling, was worked up as in the preceding experiments. Yield of trimethylphosphine oxide 54% (75), of triethylphosphine oxide 56%, of tri-n-butylphosphine oxide 66% (88). Figures in brackets are yields of crude products.

SUMMARY

Reaction of benzyl iodide or chloride with phosphorus diiodide (or red phosphorus in presence of a small quantity of iodine or phosphorus diiodide) gives tribenzylphosphine oxide and a small quantity of dibenzylphosphinic acid. Reaction of alkyl iodides with phosphorus diiodide or red phosphorus in presence of catalytic quantities of iodine gives trialkylphosphine oxides in good yields. Direct alkylation of yellow or red phosphorus by alkyl iodides actually proceeds through the step of formation of phosphorus diiodide. Alkylation of phosphorus triiodide also proceeds through the step of formation of phosphorus diiodide.

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DERIVATIVES OF TRIAZINE

II. COLOR CHARACTERISTICS OF SOME TRIAZINE MONOAZO DYES CONTAINING ACTIVE CHLORINE ATOMS

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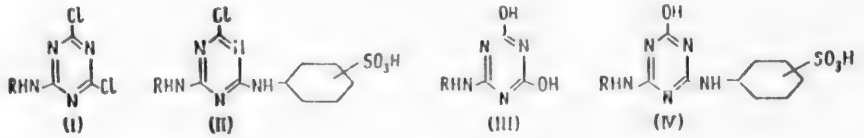
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1981-1985,
June, 1960
Original article submitted April 25, 1959

In the preceding communication [1] it was shown that an imino group situated between a triazine ring and a phenyl group has a small hypsochromic influence on the color of triazine azo dyes.

In the present work we present data characterizing the color characteristics of some triazine monoazo dyes, namely derivatives of 2,4,6-trichloro-1,3,5-triazine in which two chlorine atoms attached to the triazine remain unchanged or one chlorine atom remains intact, while the other is substituted by anilinemono- or disulfonic acid. Observations are also reported on the color of products of alkaline hydrolysis of the dyes in question.

Dyes containing unsubstituted chlorine atoms attached to triazine are of great practical importance as representatives of a new class of "reactive" dyes [2, 3] which form a covalent bond with cellulose [4-6]. Their interaction with the cellulose fiber takes place during dyeing and leads to formation of an ether-like compound of cellulose and dye [4, 7] which in a number of cases is extremely resistant to aqueous solutions of acids and alkalies. Participating in the reaction are the mobile chlorine atoms linked to triazine and the primary hydroxyls of cellulose [7].

Compounds investigated in the present work are those with the general formulas (I) and (II), as well as products of their hydrolysis, i.e., compounds corresponding to formulas (III) and (IV).



The "dyeing portion of the molecule," i.e., R, was produced with use of dyes from m-phenylenediamine-sulfonic acid and arylpyrazolones and the 1 : 1 copper complex of the dye (2-aminophenol-4-sulfonic acid → → 2,5-aminonaphthol-7-sulfonic acid) (V). These dyes were prepared by the following procedures.

Dyes of type (I) with participation of m-phenylenediaminesulfonic acid and arylpyrazolones were obtained by acylation with cyanuric trichloride of m-phenylenediaminesulfonic acid, diazotization of the resulting product and coupling, in the case of dye (VI), with 1-phenyl-3-methyl-5-pyrazolone-4'-sulfonic acid, and in the case of dyes (VIII) and (IX) by coupling respectively with 1-(2'-chlorophenyl)-3-methyl-5-pyrazolone-5'-sulfonic acid and 1-(2',5'-dichlorophenyl)-3-methyl-5-pyrazolone-4'-sulfonic acid. A dye of the same type but synthesized with participation of the copper complex (V), i.e., dye (X), was obtained by acylation of the azo compound—copper complex in question with cyanuric trichloride. Dyes with the same dyeing component but of

Name of dye	pH 6		pH 10	
	λ_{max} (mμ)	ε · 10^{-4}	λ_{max} (mμ)	ε · 10^{-4}
Dye (VI)	385	2.2	385	2.2
Hydrolyzed dye (VI)	385	2.2	385	2.2
Dye (VIII)	405	1.8	400	1.9
Hydrolyzed dye (VIII)	400	1.5	400	1.5
Dye (IX)	400	1.7	395	1.8
Hydrolyzed dye (IX)	360	1.3	370	1.8
Dye (X)	530	3.3	—	—
Hydrolyzed dye (X)	530	3.2	530	3.2
Dyes (XI-XIV)	530	3.6	530	3.6
Hydrolyzed dyes (XI-XIV)	530	3.6	530	3.6

type (II) were synthesized by reaction of dye (X) with, respectively, sulfanilic acid (dye XI), metanilic acid (dye XII), orthanilic acid (dye XIII), and aniline-2,5-disulfonic acid (dye XIV).

Dyes of types (III) and (IV) were prepared by hydrolysis of dyes (V) and (VIII-XIV) in an aqueous alkaline medium under conditions promoting complete replacement of chlorine by hydroxyl.

All the above-mentioned dyes of types (I), (II), (III) and (IV) were examined by spectrophotometry. Measurements were made of the absorption spectra in the 300-540 mμ region of aqueous solutions of dyes in molar concentrations close to 3×10^{-5} at pH values of 6 and 10. Results are set forth in the table.

We see from the table that in some cases (VI, X-XIV) the dyes exhibit maximum absorption regardless of the pH of the spectrophotometered solution and of the substituents attached to the triazine ring. In some cases (VIII and IX) the λ_{max} depends on the pH of the medium and on the character of the substituents attached to the triazine. An expecially marked hypsochromic effect arises on replacement of the chlorine attached to the triazine by hydroxyl in the case of dye (IX) obtained with participation of 1-(2',5'-dichlorophenyl)-3-methyl-5-pyrazolone-4'-sulfonic acid.

In some cases the optical absorption density does not alter on replacement of chlorine by hydroxyl; in other cases it is slightly lowered; replacement of chlorine by anilinemono- or disulfonic acid increases the density. In some cases the optical density is influenced also by the pH of the solution.

It seemed plausible to explain the considerable hypsochromic effect of alkaline hydrolysis of dye (IX) by replacement of the chlorine in the 5' position of the arylpyrazolone by hydroxyl. A similar hydrolysis is observed when dye (IX) is boiled with hydrochloric acid. Analytical data for the dye isolated after alkaline hydrolysis of dye (IX), however, did not support this explanation. Under our experimental conditions the chlorine in the 5' position remains intact on hydrolysis of dye (IX).

The considerable hypsochromic effect of alkaline hydrolysis of dye (IX), as well as the small effect in the case of dye (VIII), is evidently associated with lactam–lactim tautomerism of the dihydroxytriazine or with keto–enol tautomerism of the pyrazolone, development of which to a greater or lesser extent is promoted by substituents in the arylpyrazolone.

In the light of the results obtained, doubts must arise about the validity of the widely held view that the triazine ring completely eliminates the reciprocal action of the chromophoric systems to which it is linked. Although our data are not supported by examples in which chromophoric systems are linked through the triazine ring, they do permit us to postulate that the triazine ring does not form a barrier to interaction of the systems linked to it. This point is brought out with especial clarity in the case of dye (IX).

EXPERIMENTAL

Dyes (VI), (VIII) and (IX). Acylation of m-phenylenediaminesulfonic acid by cyanuric chloride and diazotization of the product of acylation were performed for all three dyes under different conditions.

To a solution of 2.68 g of 70.4% m-phenylenediaminesulfonic acid in 40 ml of water, cooled to 0-2°, was added with vigorous stirring 1.84 g of finely pulverized 100% cyanuric cloride, and the reaction was carried out at 0-2° and a pH of 6-6.5, the latter being maintained by periodic addition of 2 N sodium carbonate solution. After completion of reaction, signalized by change of the pH of the reaction mixture, addition was made to the suspension of 5 ml of 2 N sodium nitrite solution and 4 ml of 4 N hydrochloric acid solution until the mass was weakly acid to Congo. Stirring was thereupon continued for another 30 min at 0-2°.

Coupling of the resulting diazo compound with arylpyrazolones was effected by addition, to solutions comprising 0.01 mole of pyrazolone, 25 ml of water, 5 ml of 2 N sodium carbonate solution and 4 g of sodium acetate trihydrate, of the diazo compound from 0.01 mole of m-phenylenediaminesulfonic acid. The mass was stirred at pH 4 and a temperature of 2-4° for 5-8 hr and then kept at 0-5° without stirring until the next morning.

The dyes were salted out at 0-2° with common salt added in quantity equal to 20% of the volume; the dyes were purified by repeated reprecipitation with common salt at 0-2° and pH 6; they were dried by displacement of the mother liquor with alcohol at 0° and subsequent washing with ether. The individuality of the dyes was established by chromatographic examination and by determination of their active chlorine content; the presence of common salt in the dyes was permissible.

The content of dyeing agent in the dyes was determined by reduction with vanadium sulfate in a carbon dioxide stream and by back-titration of the unreacted vanadium salt with iron ammonium alum. The content of active chlorine bound to the triazine ring was determined from the difference between the chlorine ion content found after alkaline hydrolysis of the dye and the chlorine ion content in the unhydrolyzed dye. Chlorine ion was determined by potentiometric titration with silver nitrate under the usual conditions. The instrument used was an LP-5 potentiometer.

Agreement between the active chlorine content found in the dye and that calculated after allowance for the dyeing agent content in the same preparation was evidence of the absence from the sample of any hydrolyzed dye.

Hydrolysis of dyes (VI), (VIII) and (IX). A solution of 0.5 g of dye, 50 ml of water and 1 g of sodium hydroxide was refluxed for 2 hr on a boiling water bath. The resulting solution was quantitatively transferred to a measuring flask of 200 ml capacity, and made up to the mark with distilled water.

Chlorine ion in 50 ml of the solution was determined after addition of nitric acid until acid to Congo by potentiometric titration.

Dye (X). The starting aminoimino dye was prepared in the usual manner—by coupling of diazotized 2-aminophenol-4-sulfonic acid with J-acid in a soda—alkali medium; the dye was purified by reprecipitation. To a uniform suspension of 13.7 g of a 32% paste of the purified aminomonoazo dye in 200 ml of water (heated to 90°) was added an aqueous solution of copper sulfate tetramine prepared from 2.5 g of copper sulfate pentahydrate, 12 ml of 25% ammonia and 12 ml of water. The resulting mixture was stirred for an hour at 95-98° (under a reflux condenser). Addition was then made of 40 g of sodium chloride. After 30-min stirring, the copper complex of the dye was filtered off. The paste was thoroughly pressed and washed with hot 10% sodium chloride solution. The completeness of complex formation was confirmed by comparison of the analytical data for content of dye substance and copper. The content of the latter was determined by iodometry in the solution obtained after decomposition of the dye with potassium permanganate in a medium of concentrated sulfuric acid followed by removal of unreacted permanganate by oxalic acid.

Acylation was effected by addition, to a solution of 4.77 g of 52.4% (0.005 mole) of the prepared copper complex in 100 ml of water (cooled to 2°), of 0.92 g (0.005 mole) of cyanuric chloride with vigorous stirring. Stirring was continued for 2 hr at pH 6. The dye was salted out at 0-2°, purified by reprecipitation from aqueous solution at 0-2°, and dried by displacement of the mother liquor with acetone. The individuality of the dye was established from the contents of N = N, Cu and covalently bound chlorine. Analytical methods were the same as those described above.

Dyes (XI), (XII), (XIII) and (XIV). To a solution of acylation product, obtained under the conditions of the preceding experiment, was added a solution of 0.005 mole of sulfanilic, metanilic, orthanilic or aniline-2,5-disulfonic acid, 10 ml of water and 2.5 ml of 2 N sodium carbonate solution. The resulting solution was stirred for 8 hr at 20-25° and then stood without stirring for 30 hr at pH 6. Separation of the dye, purification drying, analyses and hydrolysis were performed under the conditions of the preceding experiment.

Light absorption by aqueous solutions of the dyes was determined with the SF-4 spectrophotometer.•

SUMMARY

1. A series of triazine monoazo dyes was synthesized that contained one or two active chlorine atoms linked to the triazine ring; the dyes and the products of their alkaline hydrolysis were characterized by their absorption spectra in the visible region.

2. It was shown that in some cases replacement of the triazine-linked chlorine by hydroxyl or by an anilinemono- or disulfonic acid does not affect the λ_{max}; in some cases the pH of the spectrophotometered solution also does not influence the λ_{max}.

3. The hypsochromic effect observed when two chlorine atoms, linked to triazine, are replaced by hydroxyl in dyes synthesized with participation of 2'-chloro- and 2',5'-dichloro derivatives of arylpyrazolone is evidently associated with lactam–lactim tautomerism of the triazine and keto–enol tautomerism of the pyrazolone.

4. The experimental data permit the conclusion that the triazine ring is not always a barrier to interaction in systems whose components are separated by it.

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A NEW SYNTHESIS OF CROTYLAMINE

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1985-1986
June, 1960
Original article submitted May 25, 1959

Crotylamine has been prepared by reduction of crotonaldoxime by sodium amalgam [1] and lithium aluminum hydride [2], by splitting-out of hydrogen halides from the corresponding halogenated butylamines [4-6] and by Gabriel's method [3, 7, 8]. Particularly worthy of attention is a paper describing the preparation in the pure state of cis- and trans-crotylamines [3]. The patent literature also contains a few communications on the preparation of crotylamine [9, 10].

In the present work we describe a simple route to pure crotylamine on the lines of the preparation of allylamine [11, 12]. The salt obtained by interaction of crotyl bromide with urotropine was subjected to hydrolysis by hydrochloric acid in a medium of alcohol, and the resulting crotylamine hydrochloride was converted to the free base.

In a medium of methylene chloride the yield of salt is 90%; in chloroform it is only 30%, probably due to the higher solubility of urotropine in chloroform (13.7 g in 100 ml at 20°) than in methylene chloride (5.3 g in 100 ml at 20°). Reaction in chloroform goes more vigorously and is probably accompanied by secondary processes.

EXPERIMENTAL•

Into 1 mole of urotropine, suspended in 800 ml of methylene chloride, was run 1 mole of crotyl bromide at a temperature not higher than 20°. Toward the end of the addition the temperature rose to 25-30°. After 15 min, the salt was cooled, filtered and dried in the air. M.p. 141° (decomp.). Yield 240 g (87% calculated on the crotyl bromide).

The salt was treated with a mixture of 96% alcohol (645 ml) and hydrochloric acid (220 ml, d 1.19) in a three-necked flask equipped with stirrer, sloping condenser and thermometer. The salt dissolved quickly when heated on a water bath and two layers formed in the mixture. The upper layer consisted of diethylformal and the lower one of crotylamine hydrochloride, alcohol, hydrochloric acid and secondary reaction products. The diethylformal was distilled off (until the upper layer disappeared), the residue was cooled and the ammonium chloride separated by filtration. The filtrate was subjected to fresh treatment with a mixture of alcohol (255 ml – 20% excess) and hydrochloric acid (70 ml). The solution was separated from the ammonium chloride and again treated with alcohol–acid mixture in volume equal to the volume of distillate from the second treatment. The treatment was repeated until the odor of diethylformal had disappeared. In practice three treatments are quite adequate. The filtrate from the third treatment was evaporated on a water bath (or in vacuo), the ammonium chloride being periodically separated by filtration after cooling of the solution.

The viscous liquid, completely free of ammonium chloride, was poured with cooling into 50% aqueous sodium hydroxide solution (240 ml). After complete separation into layers, the top layer (73 g) was collected, well dried over solid potassium hydroxide (in a refrigerator) and distilled through a dephlegmator. The 82-85°

• Work completed in 1957.

fraction weighed 35.5 g and contained 97% of amine (found by titration in presence of Bromthymol blue). Further drying and redistillation gave 23.2 g (37.5%) of crotylamine. B.p. 83.6-84.2° at 769 mm, $n^{20}D$ 1.4320; picrate with m.p. 158.3-159.0° (from ethanol).

Literature data: b.p. (trans) 83-84°, $n^{26}D$ 1.4263 [3], $n^{20}D$ 1.43167 [6]; picrate: m.p. 156.5-157.5° [2].

In the infrared spectrum• of crotylamine were found absorption bands of C—H and the methylene group (3.39 and 6.90 mμ), methyl group (7.25 mμ), amino group (2.96, 2.99 and 6.34 μ) and others (8.92, 9.27, 9.55, 11.29 and 12.16 μ).

An absorption band characterizing the double bond was not detected. All these results agree with spectral data for trans-crotylamine [3].

SUMMARY

A simple method for preparation of trans-crotylamine was developed.

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•Measurements by I. N. Shokhor.

THIOINDIGOID DYES

V. INFLUENCE OF METHYL GROUPS AND HALOGEN ON THE COLOR OF THIOINDIGO

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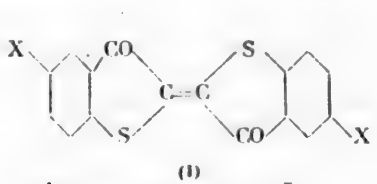
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1987-1989,
June, 1960
Original article submitted June 3, 1959

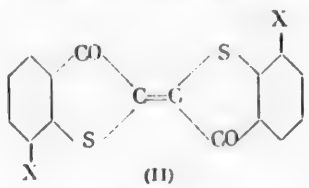
Simultaneous introduction into the thioindigo molecule of a halogen and a methyl group leads, in the event of substitution in the 5 and 7 positions, to intensification of the color of the dye [1, 2]. According to the literature, however, a methyl group in the 7 position heightens the color [3, 4]; thus, thioindigo in xylene has λ_{max} 525 mμ, 5,5'-dimethylthioindigo has 561.5mμ and 7,7'-dimethylthioindigo has 494 mμ.

It was therefore of interest to measure and compare the absorption spectra of derivatives of thioindigo substituted in the 5,5' or 7,7' positions only by halogen or methyl groups. Dyes of the formulas (I) and (II) were prepared and purified; of these, 7,7'-diiodothioindigo has not previously been described.



(I)

where X = CH_3, Cl, Br, I.



(II)

The last-named was synthesized from o-iodoaniline which was transformed by diazotization and treatment with potassium ethylxanthate into the corresponding ethylxanthic ester. Saponification of the ester by alkali and addition of chloroacetic acid at once gave S-(o-iodophenyl)-thioglycolic acid. Treatment of the acid chloride with anhydrous aluminum chloride gives 7-iodo-3-hydroxythionaphthene whose oxidation with potassium ferricyanide leads to 7,7'-diiodothioindigo.

In the table are set forth the maxima of the absorption spectra of solutions of all the dyes concerned in benzene. It follows from the data in the table that a methyl group in positions 5 and 7 deepens the color of thioindigo.

The weaker action of substituents in position 7 is probably associated with loss of coplanarity of the molecule.

With respect to deepening action the halogens are in the order of I > Br > Cl; a methyl group in the 5 position has a weaker deepening effect than halogens; that in the 7 position has a stronger deepening effect. This difference is evidently the consequence of a lowering of the effect of conjugation for the halogens with the unshared electron pair of the sulfur atom and of an increase of the inductive effect in position 7 by comparison with position 5.

Name of dye	λ_{max}	$\epsilon_{max} \cdot 10^{-4}$
Thioindigo	545	1.6
5,5'-Dimethylthioindigo	558	1.4
5,5'-Dichlorothioindigo	559	1.6
5,5'-Dibromothioindigo	559	1.7
5,5'-Diiodothioindigo	562	1.6
7,7'-Dimethylthioindigo	551	1.5
7,7'-Dichlorothioindigo	545	1.5
7,7'-Dibromothioindigo	546	1.5
7,7'-Diiodothioindigo*	548	1.3

*One additional maximum in the spectrum λ_{max} 508 mμ, ϵ_{max} $0.92 \cdot 10^{-4}$) evidently corresponds to the cis-form of the dye.

EXPERIMENTAL

The following were prepared in accordance with the literature: 5,5'-dimethylthioindigo [5], 5,5'-dichlorothioindigo [6], 5,5'-dibromothioindigo [7], 5,5'-diiodothioindigo [8], 7,7'-dimethylthioindigo [9], 7,7'-dichlorothioindigo [10] and 7,7'-dibromothioindigo [11]. All the dyes were purified by crystallization from nitrobenzene.

S-(o-Iodophenyl)-thioglycolic acid. To a solution (heated to the boil) of 7.5 ml of hydrochloric acid (d 1.15) in 25 ml of water was added 4.38 g of o-iodoaniline. The mixture was stirred for 5 min and cooled to 0°. At this temperature diazotization was effected with 5.5 ml of 4 M $NaNO_2$. Excess of nitrous acid was destroyed with urea and the diazo solution slowly run into a solution of 3.8 g of potassium ethylxanthate and 7.5 g of sodium carbonate in 25 ml of water heated to 70°. After the mixture had cooled, the precipitated oil was extracted with ether, the ether was evaporated off completely, and 25 ml of alcohol and 3 g of sodium hydroxide were added to the residual oily substance. The mixture was refluxed for 3 hr on a water bath. To the solution was added 4.5 g of chloroacetic acid in 15 ml of water, and boiling was continued for 10 min. The alcohol was distilled off and the residue diluted with 100 ml of water. The solution was filtered and the filtrate acidified to bring down S-(o-iodophenyl)-thioglycolic acid; yield 4.65 g (79.5%); m.p. 96-102°. Colorless crystals from benzene, m.p. 111.5-112.5°.

Found %: C 32.72, 32.50; H 2.75, 2.38; S 10.91, 11.12. $C_8H_7O_2IS$. Calculated %: C 32.67; H 2.40; S 10.90.

7-Iodo-3-hydroxythionaphthene. A mixture of 3 g of S-(o-iodophenyl)-thioglycolic acid, 20 ml of chlorobenzene and 1.0 ml of phosphorus trichloride was heated to 70° and held at this temperature for half an hour. The mass was cooled to 20° and 2 g of anhydrous aluminum chloride added. After being held at room temperature for 4.5 hr, the mass was poured onto ice and distilled with steam for separation of first the chlorobenzene and then the 7-iodo-3-hydroxynaphthene. Yield 1.06 g (37.5%); m.p. 145-147°; yellowish crystals. M.p. 151-152.5° (from benzene–n-hexane mixture).

Found %: C 34.88, 34.93; S 11.41, 11.42. C_8H_5OIS. Calculated %: C 34.80; S 11.61.

7,7'-Diiodothioindigo. To a solution of 0.5 g of 7-iodo-3-hydroxythioindigo in 30 ml of 1% sodium hydroxide solution was added 1.5 g of $K_3Fe(CN)_6$. The mixture was heated to the boil. The resulting dye was filtered and washed with water and alcohol. Yield 0.35 g (70%) of dye in the form of a red powder. Red needles after crystallization from nitrobenzene.

Found %: C 35.12, 35.21; H 1.19, 1.12; S 11.62, 11.83. $C_{16}H_6O_2I_2S_2$. Calculated %: C 35.05; H 1.10; S 11.70.

The absorption spectra of the dye solutions were measured with a self-recording SF-2 m spectrophotometer.

SUMMARY

1. Absorption spectra of solutions of 5,5'- and 7,7'-dimethyl- and dihalosubstituted thioindigoes were measured and it was shown that in all cases the substituents shift the absorption maximum toward longer waves, the methyl group in the 5 position deepening the color more weakly than halides, and that in the 7 position more strongly than the halides.

2. The following were prepared for the first time: 5-(o-iodophenyl)-thioglycolic acid, 7-iodo-3-hydroxythionaphthene and 7,7'-diiodothioindigo.

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DERIVATIVES OF BENZO-(c,d)-INDOLINE

V. MONOMETHINECYANINE DERIVATIVES OF BENZO-(c,d)-INDOLINE

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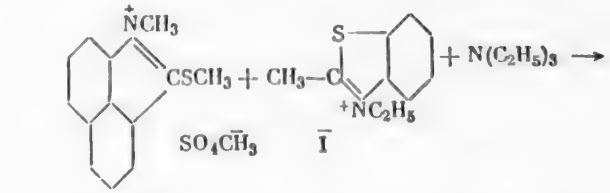
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1989-1992, June, 1960
Original article submitted April 13, 1959

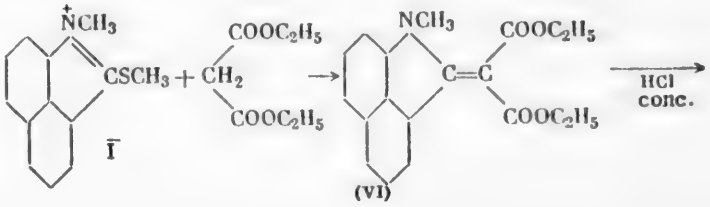
Previous communications [1, 2] described dyes of the merocyanine type obtained by condensation of N-methyl-2-methylthiobenzo-(c,d)-indolinium methosulfate with compounds containing an active methylene group. Reaction under similar conditions of N-methyl-2-methylthiobenzo-(c,d)-indolinium methosulfate or iodide with alkyl iodides of 2-methyl-substituted heterocyclic bases gave monomethinecyanine derivatives of benzo-(c,d)- indoline. Reaction of N-methyl-2-methylthiobenzo-(c,d)-indolinium methosulfate with 2-methylbenzothiazole ethiodide gave a red-violet dye (I).



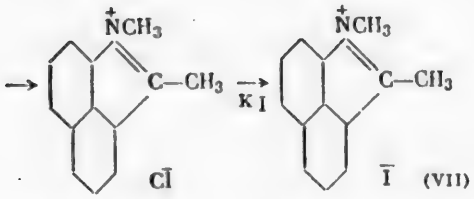
(I)

Condensation with 2-methylquinoline and 2-methylbenzoxazole ethiodides and with 2,3,3-trimethylindolenine methiodide gave red dyes (II, III, IV) of various shades.

An attempt to obtain a symmetrical monomethinecyanine by reaction of N-methyl-2-methylthiobenzo-(c,d)-indolinium iodide with malonic acid in alcohol or pyridine by Kendall's method [3] gave a blue dye which could not be isolated in the pure state. For preparation of this dye, we synthesized 2-methylbenzo-(c,d)-indolenine methiodide (VII) by the scheme:



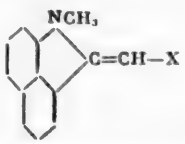
(VI)

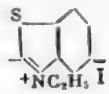
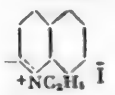
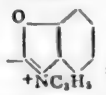
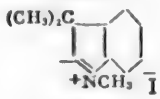
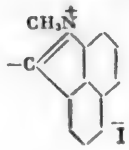


(VII)

Compound (VII) reacts smoothly with N-methyl-2-methylthiobenzo-(c,d)-indolinium iodide with formation of a blue symmetrical monomethinecyanine (V). The color of this dye is considerably deeper than that of symmetrical cyanines derived from other heterocycles (quinoline, benzothiazene, benzoxazole, 3,3-dimethylindolenine) [4]. Dyes (I, II, IV, V) have one fairly sharp maximum in the visible region. Dye (III) has two absorption maxima of similar intensities (see Table 1). The synthesized dyes have good solubility in alcohol and methanol; they color nitron.

TABLE 1

Dyes 

Compound	Structure of X	λ_{max} (in mm)	$\varepsilon \cdot 10^{-4}$
(I)		554	3.22
(II)		569	4.19
(III)		497, 531	3.69, 3.17
(IV)		535	3.14
(V)		645	3.73

EXPERIMENTAL

Monomethinecyanines (I-V). Equimolar quantities (approx. 0.02 mole) of N-methyl-2-methylthiobenzo-(c,d)-indolinium methosulfate [dyes (I, II, III)] or iodide [dyes (IV, V)] and the appropriate quaternary salt of the 2-methyl-substituted heterocyclic base were boiled for 30 min in a medium of anhydrous alcohol (4-5 ml) in presence of a slight excess of triethylamine (0.024 mole). After cooling, the dye was filtered; in the case of dye (IV) the mass was first diluted with water, and in the case of (V), it was diluted with benzene. Dyes (I, II, III, V) were purified by three crystallizations from dilute methanol; dye (IV) was crystallized three times from water. Properties and analyses are set forth in Table 2.

TABLE 2

Compound	Yield of unpurified dye (%)	Melting point	Empirical formula	Result of analysis (calculated values in brackets)
(I)	51	276—277.5°	$C_{22}H_{19}N_2IS$	N 6.04, 6.28 (5.96); S 6.86, 6.85 (6.82)
(II)	65	266—267	$C_{24}H_{21}N_2I$	C 62.46, 62.42 (62.12); H 5.05, 5.08 (4.52); I 27.16, 27.18 (27.34)
(III)	10	275—276	$C_{22}H_{19}ONI$	C 58.98, 59.00 (59.16); H 4.60, 4.50 (4.18); I 27.07, 27.00 (27.94)
(IV)	50	247.5—249.5	$C_{24}H_{23}N_2I$	N 5.98, 5.94 (6.01)
(V)	82	Does not melt at 400°	$C_{25}H_{19}N_2I$	C 63.15, 63.32 (63.31); H 4.17, 4.13 (4.01); I 26.18, 26.47 (26.77)

2-Di-(ethoxycarbonyl)-methylene-N-methylbenzo-(c,d)-indoline (VI). A mixture of 2.0 g of N-methyl-2-methylthiobenzo-(c,d)-indolinium iodide, 1.04 g of malonic ester, 0.59 g of triethylamine and 2 ml of anhydrous alcohol was boiled for 30 min. The mass was cooled in ice for 2 hr and then filtered. Yield 1.54 g (77%); three recrystallizations from dilute methanol gave 0.52 g of (VI); orange crystals with m.p. 137-138° (from dilute methanol).

Found %: N 4.50, 4.44. $C_{19}H_{19}O_4N$. Calculated %: N 4.31.

2-Methylbenzo-(c,d)-indolenine methiodide (VII). A mixture of 0.23 g of (VI) and 3 ml of concentrated hydrochloric acid was heated for an hour on a boiling water bath and then evaporated to a volume of 1 ml. A solution of 1.5 g of potassium iodide in 1 ml of water was then added. The product was cooled, filtered, washed in succession with small quantities of water, methanol and benzene. Yield of (VII) 0.17 g (78%); orange crystals.

Found %: C 50.00, 50.18; H 3.97, 4.30; N 4.43, 4.45; I 41.25, 41.0. $C_{13}H_{12}NI$. Calculated %: C 50.51; H 3.88; N 4.53; I 41.06.

SUMMARY

1. Symmetrical and unsymmetrical monomethinecyanines, derivatives of benzo-(c,d)-indoline, were prepared.

2. 2-Methylbenzo-(c,d)-indolenine methiodide was synthesized.

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HOESCH'S SYNTHESIS

PREPARATION OF BENZORESORCINOL

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1992-1996,
June, 1960
Original article submitted May 6, 1959

Dihydroxy and alkoxy derivatives of benzophenone are now used industrially as polymer stabilizers. These compounds can be synthesized by Hoesch's reaction from hydroxybenzenes and aromatic nitriles. Yields, however, are generally unsatisfactory. Benzoresorcinol (2,4-dihydroxybenzophenone), for example, was previously obtained in a yield not exceeding 40% [1, 2]. An investigation of Hoesch's synthesis led us to the observation of some previously unknown characteristics of the reaction and enabled us to considerably increase the yield of end product.

It is generally assumed [2] that Hoesch's reaction starts with interaction of a nitrile with hydrogen chloride to form an imidochloride $RC\begin{matrix}\diagup\!\!=NH\\ \diagdown\ Cl\end{matrix}$, which reacts further with the phenol to give the hydrochloride of the ketimine. The product of hydrolysis of the latter is the ketone. Comparatively recent data, however, suggest that an imidochloride is not an intermediate in Hoesch's reaction. According to these data, imidohalides of ordinary aliphatic and aromatic acids do not actually exist: at the instant of their formation they combine with a second molecule of hydrogen halide to form compounds with salt-forming properties—apparently imido dihalides [3]. It is also known that hydrogen halides, like other acidic substances, catalyze some reactions of addition to the nitrile group without intermediate formation of stable products of reaction of nitriles with acids [4].

In the light of these data, two mechanisms of Hoesch's reaction may be advanced. One possibility is intermediate formation of the imido dichloride (1) which then reacts with the phenol (2):

$$RCN + 2HCl \rightleftarrows \left[RC\begin{matrix}\diagup\!\!=NH_2\\ \diagdown\ Cl\end{matrix}\right]^+ Cl^- \qquad (1)$$

$$\left[RC\begin{matrix}\diagup\!\!=NH_2\\ \diagdown\ Cl\end{matrix}\right]^+ Cl^- + C_6H_4(OH)_2 \longrightarrow \left[R-\underset{\underset{NH_2}{\|}}{C}-C_6H_3(OH)_2\right]^+ Cl^- + HCl \qquad (2)$$

$$\downarrow H_2O$$

$$R-\underset{\underset{O}{\|}}{C}-C_6H_3(OH)_2$$

According to the second mechanism, an unstable complex of nitrile and hydrogen chloride is formed (3) in which the electrophilic character of the nitrile carbon is intensified, thereby facilitating formation of a valence bond between the electron-accepting atom of carbon of the nitrile group and the electron-donating carbon atom of the phenol (4):

$$RC\equiv N + HCl \rightleftarrows RC\equiv N\ldots HCl \qquad (3)$$

$$RC\equiv N\ldots HCl + C_6H_4(OH)_2 \longrightarrow \left[R-\underset{\underset{NH_2}{\|}}{C}-C_6H_3(OH)_2\right]^+ Cl^- \qquad (4)$$

Imido dichlorides are known to be stable only at very low temperatures, dissociating at higher temperatures into the original components. The first of the two schemes (1, 2) therefore appeared plausible in the past at low temperatures. Indeed in some cases a lowering of the temperature to 0° favors the Hoesch synthesis [2]. On the other hand other publications [5] indicate a favorable influence of rise of temperature on the synthesis, e.g., to a level (70°) far higher than the temperature of dissociation of products of interaction of nitriles with hydrogen halides. In this case the reaction can proceed by the second mechanism (3, 4). It must be assumed that in the majority of cases investigated at about room temperature or below, the reaction involves both mechanisms at the same time and with formation of other intermediate products. Reaction by the first mechanism evidently goes more slowly, but it involves less probability of secondary reactions. Depending on the character of the components, sometimes the first and sometimes the second route will apply. We believe that by altering the conditions, the reaction can be steered predominantly in one direction.

We applied these ideas to the synthesis of benzoresorcinol. When this was prepared under the literature conditions [1] (admission of hydrogen chloride in ethereal solution of benzonitrile and resorcinol at room temperature), a voluminous precipitate was formed in the course of 2-3 days, but the yield of ketone was nevertheless insignificant. The precipitate was found to contain not only the ketimine hydrochloride, but also the latter in molecular combination with benzonitrile, resorcinol and hydrogen chloride. Carefui washing with benzene led to isolation from the precipitate of mainly benzonitrile; subsequent washing with ether removed resorcinol. The composition of the molecular compounds could not be determined since the contents of benzonitrile, resorcinol and hydrogen chloride in the precipitate fluctuated sharply even in parallel experiments. It should be noted that two cases of formation of molecular compounds between nitrile and organic hydrochlorides were recently described [6, 7]. Consequently, the low yield of benzoresorcinol can be explained primarily by removal from the reaction zone of the original components together with the ketimine hydrochloride. We considered that coprecipitation of the nitrile could be prevented if the reaction could be made to proceed by the first mechanism as much as possible. According to this mechanism the nitrile forms an extremely stable chemical compound with hydrogen chloride. For this purpose the synthesis temperature was lowered to -5° and the sequence of introduction of the components into the reaction mixture was changed. As far as was possible, reactions (1) and (2) were separated in time. Hydrogen chloride was not passed into the mixture of nitrile and phenol, as usually happens, but the ethereal solution of the nitrile was treated with hydrogen chloride, and after the lapse of 2-4 hr the resorcinol was added. The latter procedure was adopted because imido dichlorides are not formed instantaneously, but sometimes in the course of several hours [6]. Finally, a study was made of the influence of zinc chloride on the course of synthesis of benzoresorcinol under various conditions. As the tabulated data show, simultaneous application of all three factors (lowering of temperature, preliminary formation of imido dichloride and use of catalyst) enabled the selectivity of the reaction to be improved (the yield of ketone relative to the quantity of precipitate was increased) and the yield of benzoresorcinol in Hoesch's synthesis to be raised to 90%.

In the presence of zinc chloride (the classic catalyst for the Hoesch synthesis) extremely pure benzoresorcinol ketimine hydrochloride came down and on hydrolysis gave a high yield of ketone. In the absence of catalyst, the above-noted molecular compounds are formed, especially if the temperature is raised and hydrogen chloride is passed into the ethereal solution of the nitrile and the phenol. Molecular compounds of ketimine hydrochloride and starting compounds are likewise precipitated during preparation of 2,4,6-trihydroxybenzophenone from benzonitrile and phloroglucinol in the absence of zinc chloride.

It was thus established that zinc chloride not only catalyzes the reaction due to its electrophilic properties, but also to some extent improves the selectivity of the Hoesch synthesis.

In the light of our observations to the effect that imido dichlorides can be primary products of the Hoesch synthesis, we are bound to draw attention to the claim [8] that these compounds cannot participate in the Hoesch synthesis. According to [8], the product of interaction of acetonitrile with two moles of hydrogen chloride, apparently acetamido dichloride, only entered into reaction with resorcinol after it had dissociated at room temperature into imidochloride and hydrogen chloride. We synthesized acetamido dichloride and studied its reaction with resorcinol. It was found that equimolar quantities of acetamido dichloride and resorcinol in the course of 6 days at −5 to 0° gave 16% of resorcinol. When the molar ratio of acetonitrile to hydrogen chloride was brought to 1 : 10, 47% of resorcinol was formed under the same conditions and even in the absence of zinc chloride. Excess of hydrogen chloride evidently shifts the equilibrium of reaction (1) to the right. When zinc chloride is present in addition to excess of hydrogen chloride, the yield of ketone rose to 77%. The

Experiments on Synthesis of Benzoresorcinol (47 ml of ether, 0.1 mole of benzonitrile, 0.1 mole of resorcinol, 1 mole of hydrogen chloride, reaction period 12 days)

Temperature	Synthesis procedure*	Weight of precipitate (in g)**	Yield of benzoresorcinol	
			(in g)	(in %)
		Without catalyst		
20—25	A	8.1	4.1	19
−7 −3	A	10.5	5.0	23
0—10	B		5.8	27***
−7 −3	B	18.4	13.0	61
		With catalyst (4 g $ZnCl_2$)		
20—25	A	12.6	6.8	32
−7 −3	A	17.5	14.1	66
20—25	B	18.7	13.5	63
−7 −3	B	23.4	19.2	89***

*A: nitrile, resorcinol, zinc chloride and ether mixed simultaneously, hydrogen chloride passed into the mixture. B: resorcinol added 2-4 hr after hydrogen chloride had been passed into the solution of nitrile and zinc chloride in ether.

**After washing with 50 ml of ethyl ether.

***Experiments described in Experimental.

possibility has thus been demonstrated of synthesis of resacetophenone via imido dichloride. Moreover the synthesis of resacetophenone is accomplished extremely smoothly and under conditions not corresponding to the first of our proposed schemes. A high yield (up to 70%) at room temperature and higher was obtained without use of procedures exerting a favorable effect on the preparation of benzoresorcinol.

EXPERIMENTAL

Preparation of benzoresorcinol. a) Dry hydrogen chloride (55 g or 1.5 moles) was passed for two hours into a stirred mixture of 15.45 g (0.15 mole) of benzonitrile and 60 ml of anhydrous ethyl ether cooled to 0°. The mass was then stood at 0° for 4 hr, after which 16.5 g (0.15 mole) of resorcinol was added and the mixture was held for 14 days at 0-10°. An abundant yellow-green precipitate appeared. After removal of the ether and hydrogen chloride, the precipitate weighed 29.6 g. It was washed with 70 ml of dry benzene. The benzene extract contained 8.1 g of benzonitrile and 1.9 g of resorcinol. The residual 19.1 g of substance was washed on the filter with 75 ml of dry ether. In the ethereal extract was found 1.9 g of benzonitrile and 6.2 g of resorcinol. The residue on the filter weighed 10.3 g and was the pure ketimine hydrochloride with m.p. 258-261° (decomp.).

Found %: Cl 14.25; N 5.78. $C_{13}H_{11}O_2N \cdot HCl$. Calculated %: Cl 14.22; N 5.62.

10 g of the ketimine hydrochloride was boiled with 100 ml of water to give 8.4 g (27%) of benzoresorcinol.

b) In the course of 50 min 36.5 g (1 mole) of dry halogen chloride was passed into a stirred mixture (cooled to 0°) of 10.3 g (0.1 mole) of benzonitrile, 4 g of anhydrous, freshly prepared and finely pulverized zinc chloride and 40 ml of anhydrous ethyl ether. The mass was then stood at 0°. After the lapse of 3 hr, 11 g (0.1 mole) of resorcinol was added and the mixture was then stood for 12 days at −7 to −3°. An abundant yellow-green precipitate appeared. After washing with 50 ml of dry ether, the precipitate weighed 23.4 g. Hydrolysis with water gave 19.2 g (89%) of benzoresorcinol.

Preparation of resacetophenone. a) Interaction of acetimido dichloride with resorcinol. A well-cooled solution of 12 g (0.1 mole) of resorcinol in 40 ml of dry ether together with 4.5 g of dry, pulverized zinc chloride

were added to 15.3 g of acetamido dichloride prepared [8] from 5.5 g (0.135 mole) of acetonitrile. The reaction mixture was stood at –7 to –3° for 6 days. Hydrolysis gave 2.6 g (16%) of resacetophenone with m.p. 145°.

b) Synthesis from acetonitrile at –7 to –3°. From 5.5 g of acetonitrile, 4.5 g of dry, pulverized zinc chloride, 12 g of resorcinol and 40 ml of dry ethyl ether (after 6 days) was obtained 14 g (77%) of resacetophenone by a method similar to the above for preparation of benzoresorcinol (Expt. b).

SUMMARY

1. Two hypotheses of the Hoesch synthesis are proposed. On the model of the synthesis of benzoresorcinol and resacetophenone, it was shown that depending on the nature of the reactants it may be expedient to operate the synthesis on the assumption that one of the mechanisms predominates.

2. It was shown that products of the Hoesch synthesis, apart from the ketimine hydrochloride, may be molecular compounds of the ketimine with nitrile, phenol and hydrogen chloride.

3. A procedure for synthesis of benzoresorcinol from benzonitrile and resorcinol in a yield of up to 90% was developed.

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•Original Russian pagination. See C. B. translation.

SOME REACTIONS OF TRIPHENYLALUMINUM

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 1996-2002,
June, 1960
Original article submitted May 18, 1959

In recent years, systems containing alkylaluminums and titanium halides have attracted great attention as they are catalysts of α-olefin polymerization. The mechanism of this type of polymerization has not been elucidated yet. In a number of papers [1-7] the opinion has been put forward that the polymerization of α-olefins in the presence of alkylaluminums and titanium tetrachloride proceeds by a radical mechanism. It seemed to us that the formation of free radicals in such systems could be detected comparatively readily if we introduced into them such a compound as triphenylaluminum since the presence of phenyl radicals in solution may be demonstrated [8, 9]. Triphenylaluminum with titanium tetrachloride has been used as a catalyst in the study of stereospecific polymerization of α-olefins [10, 11].

In this connection, it was interesting to investigate the reaction of triphenylaluminum with titanium tetrachloride in labeled benzene and the reaction of triphenylaluminum with metallic mercury and titanium tetrachloride. It was first established that there is no exchange of phenyl radicals between triphenylaluminum and labeled benzene. From the reaction mixture of deuterated benzene and triphenylaluminum, we isolated the latter as the derivative with benzalacetophenone—1,1-diphenylpropiophenone [12]. The product isolated was not deuterated, indicating the absence of exchange (Table 1).

From the reaction of triphenylaluminum with titanium tetrachloride in deuterated benzene we isolated biphenyl in an average yield of 25% on the three phenyl groups of triphenylaluminum. In all experiments, the biphenyl contained deuterium; the amount of deuterium indicated a high degree of hydrogen exchange (Table 2).

The formation of deuterated biphenyl could indicate a reaction between the solvent and free phenyl radicals formed in the given system. However, the biphenyl could also have been formed by dimerization of phenyl radicals of the complex of triphenylaluminum with titanium tetrachloride.

$$Ph_3Al + 2TiCl_4 \longrightarrow [Ph_3Al \cdot 2TiCl_4] \longrightarrow PhAlCl_2 + [2PhTiCl_3];$$
$$[2PhTiCl_3] \longrightarrow Ph_2 + 2TiCl_3.$$

The reaction scheme presented is confirmed by the fact that in another solvent, cyclohexane, the reaction of triphenylaluminum with titanium tetrachloride also leads to biphenyl. If the reaction involved the formation of a free phenyl radical, one would expect the appearance of benzene due to abstraction of hydrogen from the solvent, but not biphenyl. The hydrogen exchange observed in the reactions could have been produced by compounds containing the Al—Cl or Ti—Cl bond present in the reaction mixture [13]. In confirmation of this hypothesis, it was established experimentally that there is fast H—D exchange between biphenyl and deuterobenzene in the presence of aluminum chloride. Hydrogen exchange was not observed with titanium tetrachloride under the given conditions.

To determine conclusively whether there was reaction of free phenyl radicals of triphenylaluminum with the solvent, we carried out experiments in C^{14}-labeled benzene. If free phenyl radicals appeared, they should have reacted with the solvent, benzene, ("relay" transfer) and the biphenyl should have been active. It was

TABLE 1

Reaction of Triphenylaluminum with Deuterated Benzene (without titanium tetrachloride)

Amt. (in mmole		Reaction time (hr)	Reaction temp.	Exchange (in %)	Melting point of 1,1-diphenyl-propiophenone isolated (from alcohol)
Ph_3Al	C_6D_6				
3.88	400	25	20°	None	94°
5.40	400	15	100	None	95
5.20	400	70	20 (illumination)	None	93

TABLE 2

Reaction of Triphenylaluminum with Deuterated Benzene in the Presence of Titanium Tetrachloride (15°, reaction time 48 hr)

Expt. No.	Amt. (in mmole)			Ratio $TiCl_4/Ph_3Al$	Biphenyl yield on Ph_3Al	Exchange in biphenyl (in %)
	Ph_3Al	$TiCl_4$	C_6D_6			
1	4.0	2.0	400	0.5 : 1	14.44	11.3
2	5.0	2.6	310	0.5 : 1	9.2	11.8
3	5.4	5.6	200	1 : 1	23.7	65.1
4	4.2	7.3	310	1.75 : 1	41.8	84.0
5	7.0	22.5	400	3.2 : 1	30.5	84.1
6	2.0	8.0	290	4 : 1	25	98.0
7	2.0	7.8	200	3.9 : 1	20	No activity
8	4.0	4.7	200	1.17 : 1	20	No activity

Footnote. In Expts. 7 and 8 we used benzene labeled with C^{14}. The starting activity of the benzene in Expt. 7 was 1554 counts/min and in Expt. 8, 6355 counts/min.

found that the biphenyl contained no C^{14} at all and thus there were no free phenyl radicals in the reaction mixture. This was also confirmed by experiments in which metallic mercury was introduced into the reaction mixture. It is known that in processes involving the formation of phenyl radicals, the latter are fixed on mercury [9]. No phenylmercury compounds were found in the reaction products in our case. On the other hand, even the transfer of phenyl radicals from triphenylaluminum to mercury, which is observed in xylene solution [14], was suppressed.

The absence of free radicals in the processes examined does not exclude the possibility that other reactions of triphenylaluminum may proceed by a free radical mechanism. We considered that one such reaction could be the oxidation of triphenylaluminum by oxygen. It is known that alkylaluminums are oxidized very vigorously [15]. Arylaluminums are oxidized less vigorously, but still readily by oxygen [16]. The oxidation of these compounds has been studied very little. We attempted to investigate the oxidation of triphenylaluminum by oxygen in various solvents. In benzene solution, the reaction products contained phenol and biphenyl; in n-hexane and n-nonane, phenol alone was produced. As a result of this, it was interesting to determine the origin of the biphenyl in the oxidation of triphenylaluminum. The solvent, benzene, could have participated in the formation

TABLE 3

Oxidation of Triphenylaluminum in Various Solvents

Amt. (in mmole)		Reaction temp.	Reaction time (hr)	Found (in % on Ph_3Al)		Solvent
Ph_3Al	solvent			phenol	biphenyl	
5.0	625	15°	1.5	11.5	10.0	Benzene
5.4	625	10	1.5	10.0	3.6	
5.8	1259	10	1.5	13.0	6.6	
5.2	310	80	1.5	8.0	9.0	
6.0	340	80	8.0	11.0	13.0	
6.6	390	15	1.5	1.6	None	n-Nonane
7.3	390	10	1.5	3.3	None	
11.6	580	--50	4.0	4.3	None	n-Hexane

TABLE 4

Oxidation of Triphenylaluminum in C^{14}-Labeled Benzene and of C^{14}-Labeled Triphenylaluminum in Normal Benzene (80°, oxidation time 1.5 hr)

Expt. No.	Reagents used				Isolated from reaction							
	Ph_3Al		benzene		phenol				biphenyl			
					amount		activity		amount		activity	
	amt. (in g)	activity (counts/min)	amt. (in g)	activity (counts/min)	(in g)	% on Ph_3Al	(counts per min)	% of original	(in g)	% on Ph_3Al	(counts per min)	% of original
1	1.3	—	22	1992	0.06	4.3	303	15.2	0.2	15.3	203	10.1
2	1.3	—	12	4526	0.09	7.0	320	7.7	0.15	11.5	662	14.6
3	1.60	3040	22	—	0.08	4.7	2510	82.5	0.2	12.5	1770	58.2
4	0.65	3040	13	—	0.02	3.0	2540	83.5	0.03	5.0	2280	75.0

Footnote. The relative activity is given in Table 4. In Expts. Nos. 3 and 4, the benzene isolated after the reaction had an activity of 42 and 40 counts/min, which corresponds to 19.0 and 27.7% of the total activity of the starting triphenylaluminum.

of the biphenyl. To elucidate this point, we oxidized triphenylaluminum in C^{14}-labeled benzene and, on the other hand, oxidized C^{14}-labeled triphenylaluminum in unlabeled benzene. In the first case the phenol and biphenyl (both reaction products) were found to be active, but their activity was lower than that of the solvent, labeled benzene. In the second case, both the products, phenol and biphenyl, were active also, but their activity was less than the activity of the starting labeled triphenylaluminum. Activity appeared in the benzene in this case. The results of the investigations are given in Tables 3 and 4.

From these results it follows that the oxidation of triphenylaluminum by oxygen is very complex. In contrast to the first two reactions, it proceeds by a radical mechanism. This is indicated by the presence of "relay" transfer produced by free phenyl radicals formed by the action of oxygen on triphenylaluminum. In addition, there is another process, namely, oxidation of the solvent, benzene. It should be noted that the oxidation of triphenylaluminum proceeds very slowly. Thus, if the oxidation of Ph_3Al proceeds for a long time, the yield of the products phenol and biphenyl is almost the same as in oxidation for 1-2 hr. This retardation of the process may be explained by the inhibiting action of phenol, formed in the initial stage of the reaction. The possibility

of this effect is indicated by an experiment on the oxidation of cyclohexylbenzene with triphenylaluminum added. There was no oxidation of cyclohexylbenzene at all with this additive as in the case when pure phenol was added.

The authors would like to thank B. A. Redoshkin for carrying out this experiment.

EXPERIMENTAL

All experiments, apart from oxidation, were carried out in an atmosphere of dry, oxygen-free nitrogen. The oxidation was carried out with dry oxygen, which was dried by passage through a bottle with concentrated sulfuric acid and then four columns connected in series, each 1 m in height, containing calcium chloride, potassium hydroxide (solid), and the last two, phosphorus pentoxide deposited on asbestos.

Synthesis and isotopic analysis of starting compounds and reaction products. Triphenylaluminum was obtained by the method described by A. N. Nesmeyanov and K. A. Kocheshkov [15]. The synthesis of C^{14}-labeled triphenyl aluminum has not been described in the literature. We prepared it according to the following scheme:

$$C_6^{14}H_6 + Br_2 \longrightarrow C_6^{14}H_5Br + HBr,$$
$$C_6^{14}H_5Br + n(Hg)Na \longrightarrow (C_6^{14}H_5)_2Hg + NaBr + Hg,$$
$$3(C_6^{14}H_5)_2Hg + 2Al \longrightarrow 2(C_6^{14}H_5)_3Al + 3Hg.$$

The procedures for all stages of the process are well-known.

C^{14}-Labeled benzene was obtained by a method described in the literature [17]. Deuterobenzene was obtained by hydrogen exchange of normal benzene with deuterosulfuric acid.

Analysis for deuterium was carried out by the flotation method in which we analyzed water obtained by combustion of the compounds analyzed [18]. The C^{14} was determined by the procedure in [19]. The compound analyzed was burned to carbon dioxide, whose activity was measured with an internal-filling counter. The measurements were carried out by Yu. A. Kaplin.

1. Reaction of triphenylaluminum with deuterated benzene. a) Into a two-necked flask filled with nitrogen were introduced samples of triphenylaluminum and deuterated benzene. The flask was closed with well-ground stoppers and its contents mixed well and left for 25 hr at 20°. The flask was then connected to a condenser and the benzene evaporated to dryness in a stream of nitrogen. To the residue were added 25-30 ml of ethyl ether and the calculated amount of benzalacetophenone and then 1,1-diphenylpropiophenone was isolated as described by Wittig [12]. After recrystallization from ethanol, the 1,1-diphenylpropiophenone had m.p. 93° and was analyzed for deuterium content.

b) The reaction was carried out in a sealed glass ampule, which was heated in an electric furnace. The ampule was flushed with nitrogen (evacuated twice with subsequent filling with nitrogen). Samples of triphenylaluminum and deuterated benzene were then introduced. The contents were frozen and the ampule evacuated and sealed off. The mixture was heated at 100° for 15 hr. At the end of the experiment, the ampule was opened in a stream of nitrogen, its contents transferred with nitrogen to a flask, and then the benzene removed and the 1,1-diphenylpropiophenone isolated as described above (a and b).

c) The reaction of triphenylaluminum with deuterated benzene under the action of ultraviolet light was carried out in a quartz tube irradiated with a PRK-2 lamp. The tube was charged with the reagents (Ph_3Al and C_6D_6) in a nitrogen atmosphere, then hermetically sealed and the mixture irradiated for 70 hr. The reaction mixture was transferred to a flask with nitrogen and the benzene removed and the 1,1-diphenylpropiophenone isolated as described above.

2. Reaction of triphenylaluminum with titanium tetrachloride in deuterated benzene. Samples of triphenylaluminum, deuterated benzene, and titanium tetrachloride were introduced successively into a conical flask with a well-ground stopper in a nitrogen atmosphere. The flask was closed and the contents mixed, whereupon a brown precipitate formed immediately. The reaction was exothermal. The reaction mixture was left for 48 hr at 15°. A hydrolysis with water was then carried out. The solution was transferred to a round-bottomed flask and steam distilled. The benzene was separated from the water in the distillate, dried with

calcium chloride, and distilled from a flask with a head on a water bath. The residue contained biphenyl. After the biphenyl had been recrystallized from ethanol, its melting point and deuterium content were determined.

It should be noted that a different procedure for isolating the reaction products was also used. After the reaction, the benzene solution was filtered through a glass filter in a nitrogen atmosphere to remove the precipitate and the benzene distilled to leave biphenyl.

The reactions in cyclohexane and C^{14}-labeled benzene were carried out similarly.

3. Exchange between biphenyl and deuterobenzene in the presence of $AlCl_3$ or $TiCl_4$. These experiments were carried out under the same conditions as the reaction of triphenylaluminum with titanium tetrachloride.
a) We used 0.52 g of biphenyl, 6.0 g of deuterobenzene containing 15047 γ of deuterium, and 0.97 g of $AlCl_3$; the biphenyl was isolated and purified as in the previous experiment. We isolated 61.8% of the biphenyl used. Isotopic analysis showed that it contained 12405 γ of deuterium or 82.6% of that of the starting deuterobenzene.

b) We used 0.72 g of biphenyl, 8.6 g of deuterobenzene containing 15047 γ of deuterium, and 0.97 g of $TiCl_4$. We isolated 49.5% of the biphenyl taken containing 135 γ of deuterium or 0.9% of that of the starting deuterobenzene.

4. Reaction of triphenylaluminum with titanium tetrachloride and metallic mercury in xylene. In a nitrogen atmosphere, 100 g of metallic mercury, 80 ml of o-xylene, 1.55 g of triphenylaluminum, and 1.17 g of titanium tetrachloride (ratio $TiCl_4/Ph_3Al = 1$), were introduced into a thick-walled bottle with a well-ground stopper. The reaction vessel was shaken at 20° for 25 hr. A hydrolysis with water was then carried out. The three layers formed, mercury, water, and xylene, were separated in a separating funnel. The xylene was dried with calcium chloride and distilled. The residue was 0.2 g of biphenyl. The yield was 13.5% on Ph_3Al and after recrystallization from ethanol, the product had m.p. 69°. The organomercury compounds Ph_2Hg or PhHgCl were not detected.

5. Oxidation of triphenylaluminum with oxygen. The reaction vessel was a three-necked flask, connected by ground joints to a reflux condenser, oxygen inlet tube, and funnel for introducing solvent. The system was first flushed with nitrogen. Then a sample of triphenylaluminum was introduced into the reaction flask, followed by solvent. The funnel was then rapidly replaced by a thermometer pocket, the system adjusted to the reaction temperature by external heating or cooling, and the oxygen input begun. Triphenylaluminum is sparingly soluble in benzene [20] and therefore it was present in the reaction mixture as a precipitate at the beginning of the reaction. It completely dissolved as oxygen was introduced and a homogeneous yellow solution formed. At the end of the oxidation, the reaction mixture was treated with 5% sodium hydroxide solution and poured into a separating funnel and the aqueous alkaline layer separated from the solvent. The solvent was dried with calcium chloride and distilled. The residue was biphenyl, which after recrystallization from ethanol, was characterized by the melting point (69-70°) and a mixed melting point with pure biphenyl.

The aqueous alkaline solution was acidified with 10% sulfuric acid and steam distilled. Phenol was isolated from the distillate as tribromophenol. The latter was identified by the melting point.

It should be noted that in the isolation of C^{14}-labeled reaction products, phenol and biphenyl, we paid special attention to their purity, especially in experiments with labeled solvent. We repeatedly dissolved the biphenyl in normal benzene with subsequent distillation of the latter and repeatedly recrystallized the biphenyl and tribromophenol from ethanol. Their melting points in a sealed capillary and activities were then determined.

In the oxidation of C^{14}-labeled triphenylaluminum, before hydrolysis, part of the benzene was distilled from the reaction mixture for determination of the activity of the benzene after the reaction. The remaining solution was treated with 5% NaOH and then all the products isolated as described above.

SUMMARY

1. The reaction of triphenylaluminum with titanium tetrachloride in various solvents yielded biphenyl without the intermediate formation of free phenyl radicals. This was demonstrated by the absence of "relay" transfer of phenyl radicals with labeled benzene and also the absence of fixation of phenyl radicals on metallic mercury when the reaction was carried out in the presence of this metal.

2. The oxidation of triphenylaluminum solutions by oxygen proceeds by a free radical mechanism. This was demonstrated by the use of C^{14}-labeled triphenylaluminum and solvent benzene. It was shown that the reaction products biphenyl and phenol were obtained both from phenyl radicals of triphenylaluminum and from the solvent, benzene.

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•Original Russian pagination. See C. B. translation.

SYNTHESIS OF SOME DERIVATIVES OF Δ^2-PYRAZOLINE

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2002-2008,
June, 1960
Original article submitted May 27, 1959

In view of the very marked dependence of fluorescent properties upon the structure of derivatives of Δ^2-pyrazoline [1, 7-19, 29, 26, 27, 33], it seemed of interest to synthesize derivatives of Δ^2-pyrazoline not described in the literature, and to investigate their scintillation properties. At the same time there was a possibility of establishing a relationship in regard to the fluorescent properties of isomers which are encountered among the tri- and tetraphenyl-Δ^2-pyrazolines.

Derivatives of Δ^2-pyrazoline were synthesized by means of reactions described by Auwers [1] and Strauss [2], i.e., by the interaction of α,β-unsaturated ketones with aryl hydrazines at elevated temperatures. It is known that the velocity of cyclization of hydrazones of α,β-unsaturated ketones to form the corresponding pyrazolines depends markedly on the reaction conditions: temperature, solvent and ratio of reactants [2, 27]. A detailed study of cyclization conditions is of both theoretical and practical interest in connection with the preparation of those derivatives of Δ^2-pyrazoline which up to the present time have not been described in the literature. In some cases the preparation of only the phenylhydrazones of the corresponding unsaturated ketones has been described.

Propenylstyryl ketone, needed for preparing 1,5-diphenyl-3-propenyl-Δ^2-pyrazoline, was prepared by condensing methylpropenyl ketone [11] with benzaldehyde in an acid medium.

The literature data on the synthesis of 1,3-diphenyl-5-styryl-Δ^2-pyrazoline are extremely contradictory [3-5]. Apparently none of the authors of these papers succeeded in preparing 1,3-diphenyl-5 styryl-Δ^2-pyrazoline, although it is quite probable that Strauss [5] obtained this compound unknowingly. However, because of the weak fluorescence of his compound, he characterized it as having a seven-membered ring. 1,3-Diphenyl-5-styryl-Δ^2-pyrazoline was obtained easily by heating 4-phenylbutadienyl-(1,3)-phenyl ketone with phenylhydrazine in acetic acid. The presence of a five-membered ring in this compound was shown by Hübl's iodination method. Furthermore, this compound gave Knorr's pyrazoline reaction [28].

Klingemann [6] succeeded in preparing 1,3,4,5-tetraphenyl-Δ^2-pyrazoline by reacting phenylhydrazine with cis-α,α'-dibenzoylstilbene in acetic acid solution, but in a very small yield. Starting with benzaldesoxybenzoin [7, 12-14], we prepared 1,3,4,5-tetraphenyl-Δ^2-pyrazoline in the form of two isomers; the trans isomer in a good yield, but only a small quantity of the cis isomer, analogous to the compound described by Klingemann [6]. trans-Tetraphenyl-Δ^2-pyrazoline fluoresced more strongly than the cis form, which agrees with data cited in the literature [20, 21] on the fluorescence of cis and trans isomers.

The synthesis of 1,3,4-triphenyl-Δ^2-pyrazoline should be established more exactly. Literature data regarding this compound [29-32] are in our opinion directly related to the cis and trans isomers of derivatives of Δ^2-pyrazoline. 1,3,4-Triphenyl-Δ^2-pyrazoline with m.p. 132°, was described first by Matti and Perrier [29]. They obtained methylenedesoxybenzoin, needed in its synthesis, from α-aminodesoxybenzoin and formaldehyde. Later Mehr and Becker [30] obtained 1,3,4-triphenyl-Δ^2-pyrazoline with a similar m.p. 135-136° by reacting phenylhydrazine and methylenedesoxybenzoin in an alcoholic medium. These authors noted a yellowish-green fluorescence in the solid substance and a pale blue fluorescence in a solution under ultraviolet light. Mehr and Becker

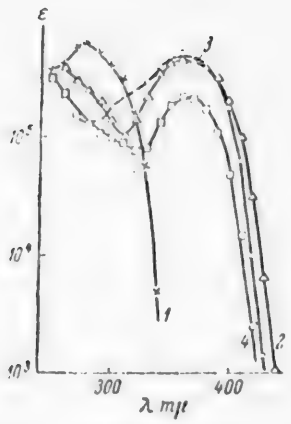

Fig. 1. Absorption spectra in dioxane (concentration 10^{-3} g per liter). 1) 1,5-Diphenyl-3-ethyl-Δ^2-pyrazoline; 2) 1-β-naphthyl-3,5-diphenyl-Δ^2-pyrazoline; 3) 1-p-tolyl-3,5-diphenyl-Δ^2-pyrazoline; 4) trans-1,3,4,5,-tetraphenyl-Δ^2-pyrazoline.

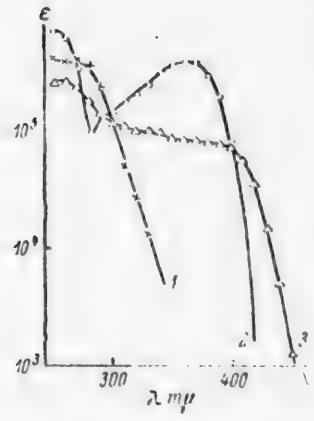

Fig. 2. Absorption spectra in dioxane (concentration 10^{-3} g per liter). 1) 1,3,4-Triphenyl-Δ^2-pyrazoline; 2) 1,3-diphenyl-5-styryl-Δ^2-pyrazoline; 3) 1,5-diphenyl-3-propenyl-Δ^2-pyrazoline.

synthesized methylenedesoxybenzoin by reacting methylmagnesium iodide and benzyl with subsequent saponification and splitting off of water from methylbenzoin [30]. In the two following papers 1,3,4-triphenyl-Δ^2-pyrazoline is described as a colorless substance with m.p. 210-211° [32], and 211-213° [31]. We synthesized 1,3,4-triphenyl-Δ^2-pyrazoline by reacting phenylhydrazine in acetic acid solution with methylenedesoxybenzoin prepared according to the method of Fisselmann and Ribka [9] with slight modifications. A colorless product with m.p. 207-208° was obtained. It exhibited a weak violet fluorescence in the crystalline state as well as in organic solvents. Undoubtedly, in this case we are dealing with two isomers of one and the same compound. On the basis of literature data [20, 21] and our own observations on the fluorescence of cis and trans isomers 1,3,4-triphenyl-Δ^2-pyrazoline with the lower melting point must be regarded as the trans isomer, while the high-melting colorless product with weak fluorescence is the cis isomer.

It is interesting to note that of all the derivatives of Δ^2-pyrazoline only the cis-1,3,4,5-tetraphenyl- and cis-1,3,4-triphenyl-Δ^2-pyrazolines do not give the well known Knorr pyrazoline reaction.

Moreover, it is necessary to point out that the preparation of several compounds described in the literature was not very successful because of unreliable literature data. For example, in Finar's description of the synthesis of 1,6-diphenylhexane-1,3,4,6-tetraone, there is an error in the ratio of the reactants. The ratio of ethyl oxalate to acetophenone should be 1 : 2 and not 1 : 1 as described in the original [8].

Methylenedesoxybenzoin was obtained in a small yield by the method of [9]. While studying this reaction we found that addition of acetic acid during the reaction improved the condensation of desoxybenzoin with formaldehyde, and a good yield was thus obtained.

In the preparation of bipyrazolyls from the above-mentioned tetraketone by Finar's method [8] a mixture of the original tetraketone and bipyrazolyl was obtained. Therefore, this method was modified so that initially all the tetraketone was dissolved in acetic acid, after which the phenylhydrazine was added. In this way a good yield of 1,1',5,5'-tetraphenyl-3,3'-bipyrazolyl was obtained, and the formation of 1,1',3',5-tetraphenyl-3,5'-bipyrazolyl, as described in the literature, was not observed.

In Figs. 1-4 are shown the absorption spectra and also the luminescence spectra of derivatives of Δ^2-pyrazoline not previously described in the literature. A detailed description of the optical characteristics of these compounds in connection with their use as additives in plastic scintillators has been given in previous communications [35, 34, 25].

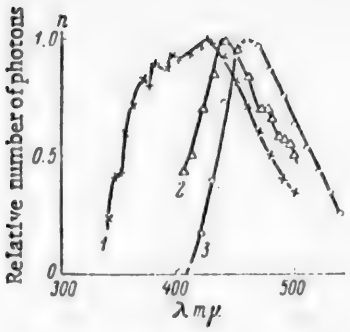

Fig. 3. Luminescence spectra in dioxane (concentration 10^{-3} g/liter). 1) 1,3,4-Triphenyl-Δ^2-pyrazoline; 2) cis-1,3,4,5-tetraphenyl-Δ^2-pyrazoline; 3) 1,5-diphenyl-3-propenyl-Δ^2-pyrazoline.

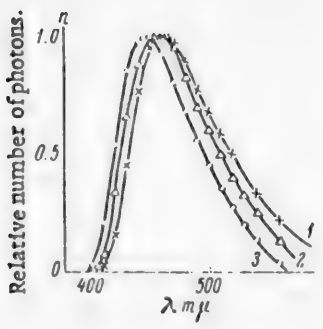

Fig. 4. Luminescence spectra in dioxane (concentration 10^{-3} g/liter). 1) 1-(β-Naphthyl)-3,5-diphenyl-Δ^2-pyrazoline; 2) 1-(p-tolyl)-3,5-diphenyl-Δ^2-pyrazoline; 3) trans-1, 3,4,5-tetraphenyl-Δ^2-pyrazoline.

EXPERIMENTAL*

Propenylstyryl ketone. A solution of 21.05 g of methylpropenyl ketone [11] in 26.6 g of benzaldehyde was saturated with hydrogen chloride over the course of 1 hr, while keeping the mixture well cooled, after which it was allowed to stand for 2 days in a refrigerator. The two layers which formed were not separated, but the whole mass was diluted with ether, treated with a saturated solution of sodium bisulfite, washed with water, and the ether solution dried with sodium sulfate. The ether was distilled off, and the residue was distilled under vacuum giving a yellow-colored oil boiling at 120-125° (1 mm). Yield 31.5%.

Chlorobenzaldesoxybenzoin [12-14]. Hydrogen chloride was passed through a solution of 10 g of desoxybenzoin in 11 g of benzaldehyde at 18-20° until a solid mass was formed. Air was blown through the reaction mass, which was then triturated in alcohol and recrystallized from acetic acid to give a colorless crystalline material with m.p. 154-155° (according to literature data the m.p. is 172° [13]).

Methylenedesoxybenzoin. To a boiling solution of 19.6 g of desoxybenzoin in 80 ml of methyl alcohol was added 30 ml of 32% formaldehyde solution, 0.5 ml of piperidine in 10 ml of methyl alcohol, and 0.5 ml of acetic acid. The synthesis and treatment of the reaction mixture were then carried out as described in the literature [9], except that ether was used for extraction instead of methylene chloride.

1,5-Diphenyl-3-ethyl-Δ^2-pyrazoline. A hot solution of 10 g of styrylethyl ketone [10] in 25 ml of acetic acid was mixed with 9 g of phenylhydrazine. The solution was then stirred and heated to 80-90° in the course of 1 hr. A solid precipitated which was separated and recrystallized from alcohol. After subliming it in a high vacuum (10^{-4} mm Hg) a colorless crystalline material with m.p. 69.5° was obtained, which gave Knorr's pyrazoline reaction. It exhibited a violet fluorescence in the crystalline state under ultraviolet light. In organic solvents its fluorescence was blue, but very much weaker than in the crystalline state. Yield 90%.

Found %: N 10.90. M 248.2. $C_{17}H_{18}N_2$. Calculated %: N 11.19. M 250.3.

All the following derivatives of Δ^2-pyrazoline were prepared by methods similar to those described above. In some cases only the temperature and the time of heating were changed.

1,3-Diphenyl-5-styryl-Δ^2-pyrazoline from 4-phenylbutadienylphenyl ketone [15] and phenylhydrazine. Yellowish-green crystals with m.p. 126-127° were obtained from a mixture of alcohol and acetone (2 : 1). Yield 78%.

Found %: N 8.10. M 323.5. Iodine No. 80.19. $C_{23}H_{20}N_2$. Calculated %: N 8.64. M 324.4. Iodine No. 78.26.

*Analyses were made by L. A. Ovakimyan.

1,5-Diphenyl-3-propenyl-Δ^2-pyrazoline was prepared from propenylstyryl ketone and phenylhydrazine in an atmosphere of carbon dioxide gas at 30-40°. Upon standing a dark red oil and white shiny crystals separated. The white crystalline substance of unknown structure melted at 220°. It was very soluble in water, but it did not fluoresce. Its mol. wt. was 623.

The oil was extracted with ether and washed with soda solution until a neutral reaction to litmus was obtained. The ether layer was dried, and after driving off the ether the residue was distilled under vacuum. The product boiled at 184-186° (0.5 mm) and gave Knorr's pyrazoline test.

Found: Mol. wt. 259.0. $C_{18}H_{18}N_2$. Calculated: Mol. wt. 262.34.

1,3,4,5-Tetraphenyl-Δ^2-pyrazoline was prepared from benzaldesoxybenzoin [14] and phenylhydrazine. The two isomers of tetraphenylpyrazoline were separated by fractional crystallization from alcohol. trans-1,3,4,5-Tetraphenyl-Δ^2-pyrazoline was the more soluble in alcohol and gave Knorr's pyrazoline test. It was a colorless substance with m.p. 152.5-153°. Yield 83%.

Found %: N 7.23. Mol. wt. 374.5. $C_{27}H_{22}N_2$. Calculated %: N 7.48. Mol. wt. 374.4.

cis-1,3,4,5-Tetraphenyl-Δ^2-pyrazoline with m.p. 213-214° did not give Knorr's test. Yield 9.2%.

Found %: N 7.30. Mol. wt. 375.2. $C_{27}H_{22}N_2$. Calculated %: N 7.48. Mol. wt. 374.4.

cis-1,3,4-Triphenyl-Δ^2-pyrazoline was prepared from methylenedesoxybenzoin and phenylhydrazine. It crystallized from a mixture of alcohol and acetone (2 : 1) as a colorless substance with m.p. 207-208°. Yield 89%. It did not give Knorr's pyrazoline test.

Found %: N 9.17. Mol. wt. 296. $C_{21}H_{18}N_2$. Calculated %: N 9.39. Mol. wt. 298.37.

1-p-Tolyl-3,5-diphenyl-Δ^2-pyrazoline was prepared from benzalacetophenone [16] and p-tolylhydrazine. Light yellow crystals with m.p. 166° were obtained from a mixture of alcohol and acetone (2 : 1). Yield 82%.

Found %: N 8.60. Mol. wt. 313.8. $C_{22}H_{20}N_2$. Calculated %: N 8.97. Mol. wt. 312.4.

1-β-Naphthyl-3,5-diphenyl-Δ^2-pyrazoline was prepared from β-naphthylhydrazine in acetic acid solution and benzalacetophenone. Light yellow crystals were obtained melting at 179.5° (dec.). Yield 83%.

Found %: N 7.78. Mol. wt. 344.2. $C_{25}H_{20}N_2$. Calculated %: N 8.03. Mol. wt. 348.4.

1,3-Diphenyl-5-furyl-Δ^2-pyrazoline was prepared from furfurylideneacetophenone [22] and phenylhydrazine. Colorless needles melting at 124° were obtained from a mixture of alcohol and acetone (2 : 1). Yield 86%.

Found %: N 9.85. Mol. wt. 285.1. $C_{19}H_{16}N_2O$. Calculated %: N 9.71. Mol. wt. 288.3.

1,4-bis-[1-Phenyl-3-methyl-Δ^2-pyrazolinyl-(5)]-benzene was prepared by heating a mixture of 1,4-bis-(β-acetylvinyl)-benzene [23] and phenylhydrazine at 90-100° for 2 hr. A colorless crystalline substance with m.p. 224-225° was obtained from pyridine. Yield 72%.

Found %: N 14.29. Mol. wt. 400.2. $C_{26}H_{26}N_4$. Calculated %: N 14.20. Mol. wt. 394.5.

1,4-bis-[1,3-Diphenyl-Δ^2-pyrazolinyl-(5)]-benzene [24] was prepared from 1,4-bis-(1-phenyl-propenone-1)-benzene (m.p. 192°; according to [24] the m.p. is 200°) and phenylhydrazine. Colorless crystals with m.p. 215° (dec.) were obtained from pyridine (m.p. given in the literature [24] is 300°). Yield 83%.

Found %: N 11.08. Mol. wt. 514.1. $C_{36}H_{30}N_4$. Calculated %: N 10.80. Mol. wt. 518.6.

1,6-Diphenylhexane-1,3,4,6-tetraone [8]. Sodium methylate, prepared from 16 g of methanol and 12.5 g of sodium, was dissolved in 300 ml of ether and mixed at 0° with 36.5 g of ethyl oxalate and one half (30 g) of the necessary acetophenone, and then after 4 hr the other half (30 g) of the acetophenone was added. The rest of the synthesis was similar to that of [8].

1,1',5,5'-Tetraphenyl-3,3'-bipyrazolyl [8] was prepared from 1,6-diphenylhexane-1,3,4,6-tetraone and phenylhydrazine by heating the mixture for 4 hr. M.p. 231°. Yield 73%.

Found %: N 12.45. Mol. wt. 439.5. $C_{30}H_{22}N_4$. Calculated %: N 12.77. Mol. wt. 438.5.

SUMMARY

1. Propenylstyryl ketone, which has not been described previously in the literature, was prepared.

2. Several derivatives of Δ^2-pyrazoline, which have not been described previously in the literature, were prepared.

3. Modifications were made in the methods of preparing several compounds described previously.

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SUBSTITUTION OF HALOGEN IN AZO COMPOUNDS

X. PREPARATION OF MONOETHERS OF 2,2'-DIHYDROXY-1,1'-AZONAPHTHALENE AND SIMPLE ETHERS OF 1-AMINO-2-NAPHTHOL

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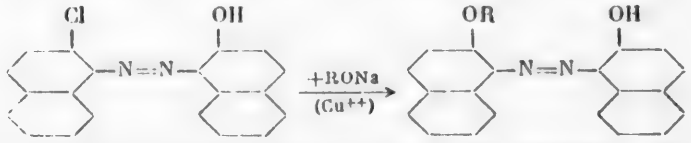
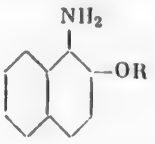
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2008-2014, June, 1960
Original article submitted June 2, 1959

Good yields of 2-alkoxy- and 2-aroxy-2'-hydroxy-1,1'-azonaphthalenes (monoethers of 2,2'-dihydroxy-1,1'-azonaphthalene) are obtained by substituting the chlorine atom in o-chloro-o'-hydroxy-azo dyes by alkoxy- and aroxy-groups by reacting 2-chloro-2'-hydroxy-1,1'-azonaphthalene (an azo dye from 1-amino-2-chloronaphthalene and 2-naphthol) with alcoholates and phenolates in the presence of copper salts [1].



R = CH_3, C_2H_5, n-C_3H_7, n-C_6H_{13}, n-C_8H_{17}, n-$C_{18}H_{37}$, $C_6H_5CH_2$, $C_6H_5CH_2CH_2$, C_6H_5, 2-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, 2,4-$(CH_3)_2C_6H_3$, 2,5-$(CH_3)_2C_6H_3$, 3,5-$(CH_3)_2C_6H_3$.

Simple ethers of 1-amino-2-naphthol are obtained by reduction cleavage of the monoethers, and are characterized by their hydrochlorides and N-benzoyl derivatives.



R = C_2H_5, n-C_3H_7, n-C_6H_{13}, n-C_8H_{17}, n-$C_{18}H_{37}$, $C_6H_5CH_2CH_2$, C_6H_5, 2-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, 3,5-$(CH_3)_2C_6H_3$.

Of these, as far as is known, 1-amino-2-ethoxynaphthalene [2] and 1-amino-2-butoxynaphthalene [3] have been described in the form of the free bases.

1-Amino-2-chloronaphthalene, necessary for synthesis of initial 2-chloro-2'-hydroxy-1,1'-azonaphthalene, was obtained by the somewhat different method of Charrier and Ferreri [4], namely, the substitution of the hydroxy-groups in 4-methoxybenzene- azo-2'-naphthol by chlorine, the action of phosphorus pentachloride and subsequent reduction cleavage of the chloro-substituted azo dye so formed.

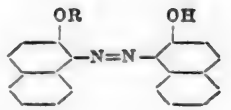
EXPERIMENTAL

(In conjunction with V. S. Zenkevich)

1-Amino-2-chloronaphthalene. 13.9 of 4-methoxybenzene-azo-2'-naphthol (an azo dye from p-anisidine and 2-naphthol, m.pt. 138-139°C, compare [5]) was carefully ground with 10.4 g of phosphorus pentachloride for 15-20 min in a porcelain mortar. The homogeneous mixture was heated for 3.5 hr in a porcelain dish on a

TABLE 1

2-Alkoxy-2'-hydroxy-1,1'-azonaphthalenes



Substance No.	R	Yield, %	Melting point	Solvent used in crystallization	Color and form of crystals	Molecular formula	Found, %			Calc., %		
							C	H	N	C	H	N
(I)	CH_3	89	189—189.5°	Glacial acetic acid	Red flat rhombi	$C_{21}H_{16}O_2N_2$	76.82, 76.44	4.96, 4.99	8.20, 8.36	76.81	4.91	8.53
(II)	C_2H_5	97	206—206.5	Benzene	Red plates	$C_{22}H_{18}O_2N_2$	76.67, 77.07	5.34, 5.39	8.24, 8.34	77.17	5.29	8.18
(III)	n -C_4H_9	97	154.5—155.5	Methyl alcohol + + benzene (4 : 3)	Red plates	$C_{24}H_{22}O_2N_2$	78.32, 78.34	6.22, 6.28	7.38, 7.22	77.81	5.98	7.56
(IV)	n -C_6H_{13}	98	152—152.5	Benzene	Red needles	$C_{26}H_{26}O_2N_2$	78.21, 78.12	6.82, 6.93	7.19, 7.13	78.36	6.57	7.03
(V)	n -C_8H_{17}	98	134.5—135.5	Acetone	Red prisms	$C_{28}H_{30}O_2N_2$	78.88, 78.80	6.74, 6.82	6.56, 6.76	78.83	7.09	6.56
(VI)	n -$C_{18}H_{37}$	73.5	117—117.2	Benzene + methyl alcohol (3 : 2)	Red plates	$C_{38}H_{50}O_2N_2$	80.14, 80.18	8.49, 8.50	5.19, 5.11	80.51	8.89	4.94
(VII)	$C_6H_5CH_2$	95	179—179.5	Benzene	Red flat needles	$C_{27}H_{20}O_2N_2$	80.35, 80.19	5.10, 5.10	7.39, 7.31	80.17	4.98	6.92
(VIII)	$C_6H_5CH_2CH_2$	99	231—232	Dichloroethane	Red needles	$C_{28}H_{22}O_2N_2$	79.88, 80.05	5.60, 5.50	7.10, 7.00	80.35	5.30	6.69

water bath at 80-90°, with constant stirring with a glass rod. The resulting semiliquid viscous product solidified on cooling, was then pulverized and ground in the cold with 30 ml of methyl alcohol. The insoluble portion was filtered off, washed with methyl alcohol and dried spontaneously. 14.3 g (96.3%) of 4-methoxybenzene-azo-2'-chloronaphthalene was obtained: brownish-red rhombohedra, not completely regular in form (from acetone), m.pt. 85-86° (in the literature [4]: m.pt. 87°).

To a boiling solution of 10 g of 4-methoxybenzene-azo-2'-chloronaphthalene in 80 ml of glacial CH_3COOH was added 28 g of zinc dust in small quantities with stirring over a period of 30 min, after which the reaction mixture was heated for a further 1.5 hr under a reflux condenser. The cooled reaction product was made alkaline with caustic soda solution until a definite alkaline reaction was given with phenolphthalein and steam distilled. 1-Amino-2-chloronaphthalene separating out from the distillate as fine, long needles was filtered off and dried over calcium chloride in a desiccator. Yield 2.8 g (46.5%), m.pt. 57-58° (in the literature [4]: m.pt. 56°). A sample mixed with p-anisidine (m.pt. 57°, see [6]) underwent a melting point depression to 33-36°.

Found %: C 67.39, 67.50; H 4.30, 4.39. $C_{10}H_8NCl$. Calculated %: C 67.60; H 4.50.

2-Chloro-2'-hydroxy-1,1'-azonaphthalene. Diazotization of 1-amino-2-chloronaphthalene was carried out at 3-6°, and combination with 2-naphtholate at 8-16° in a weakly alkaline medium. 2-Chloro-2'-hydroxy-1,1'-azonaphthalene (the initial dye) was purified by recrystallizing from glacial acetic acid; dark-red, small needles, m.p. 177.5-178°. Readily soluble in benzene, toluene, methyl, ethyl, and n-butyl alcohols, chloroform, not so readily in acetic acid, poorly soluble in acetone (even on heating). A solution of the dye in concentrated sulfuric acid had a violet-blue color.

Found %: C 72.16, 72.37; H 4.15, 4.08; N 8.44, 8.68. $C_{20}H_{13}ON_2Cl$. Calculated %: C 72.18; H 3.91; N 8.42.

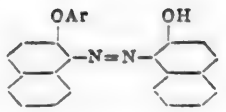
Substitution of chlorine by alkoxygroups. To a solution of sodium alcoholate, obtained by reacting 20 ml of the corresponding alcohol: methyl, ethyl, n-butyl (b.p. 117°), n-hexyl (b.p. 157°), n-octyl (b.p. 194-195°), benzyl (b.p. 204-206°), β-phenylethyl (b.p. 219-221° at 750 mm) with 0.5 g of metallic sodium, were added finely ground copper sulfate (1.5 g) and the initial dye (2 g), 10 ml of toluene was added, and the obtained mixture heated for 5-7 hr at 100-110° with stirring (in the case of methyl and ethyl alcohols, at the boiling point of the reaction mixture). To obtain the alcoholate of n-octadecyl alcohol (m.p. 58.6°) 6.5 g of it were subjected to prolonged heating with 0.5 g of metallic sodium in 20 ml of boiling xylene with vigorous stirring; toluene was not added in this instance. After heating was completed, the reaction product was diluted with water (200-300 ml) and toluene, excess of the corresponding alcohol being removed with steam. The precipitate was then filtered off and washed with boiling water. In experiments with octadecyl alcohol the reaction product was diluted with 100 ml of methyl alcohol, and the viscous product separating out was boiled twice with about 15-20 ml of methyl alcohol to remove excess octadecyl alcohol. The precipitates were then treated by boiling with 20% hydrochloric acid (50 ml) for 1 hr, the product diluted with water, the precipitates filtered off, washed free of chlorine ions, and dried at room temperature or at 60-70°. Absence of chlorine was verified by the Beilstein test.

Yields, properties, and analytic data of 2-alkoxy-2'-hydroxy-1,1'-azonaphthalenes (monoethers of 2,2'-dihydroxy-1,1'-azonaphthalene and alkyl groups) are given in Table 1. Monoethers (I), (II), and (III) are readily soluble in benzene, toluene, chloroform (III also in dichloroethane and carbon tetrachloride), poorly soluble in methyl and ethyl alcohols, acetone, acetic acid. Monoethers (IV), (V), and (VI) are highly soluble in chloroform, carbon tetrachloride, dichloroethane, chlorobenzene, less so in acetone and benzene, poorly in methyl and ethyl alcohols and acetic acid; on heating they are highly soluble in benzene and acetone. Monoether (VII) is readily soluble in chloroform and chlorobenzene, less so in benzene, toluene, acetone, poorly in methyl and ethyl alcohols and acetic acid. Monoether (VIII) is poorly soluble in chloroform, dichloroethane, chlorobenzene, insoluble in benzene, methyl and ethyl alcohols, acetone, acetic acid, carbon tetrachloride; on heating it is readily soluble in chloroform, dichloroethane, and chlorobenzene, less so in benzene and carbon tetrachloride.

Substitution of chlorine by aroxygroups. 2 g (0.006 mole) of initial dye and 1.5 g of copper sulfate, finely divided, were introduced into a solution of the corresponding sodium phenolate, obtained by reacting 0.03-0.06 mole of phenol, o-or p-cresol, 1,2,4-, 1,2,5-, or 1,3,5-xylenol with the equivalent quantity of caustic soda as a 16-39% solution. The resulting mixture was diluted with 10 ml of toluene and heated with stirring for 5-10 hr at 100-110°. On cooling, the reaction product was diluted with water (200-300 ml), toluene

TABLE 2

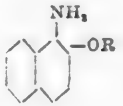
2-Aroxy-2'-hydroxy-1,1'-azonaphthalenes



Substance No.	Ar	Yield, %	Melting point	Solvent used in crystallization	Color and form of crystals	Molecular formula	Found, %			Calc., %		
							C	H	N	C	H	N
(IX)	C_6H_5	84	200.5—201.5°	Benzene	Red broad needles	$C_{26}H_{18}O_2N_2$	79.99, 79.96	4.66, 4.85	7.13, 7.27	79.97	4.64	7.17
(X)	2-$CH_3C_6H_4$	97	181—182	Pyridine + water (10 : 1)	Red plates	$C_{27}H_{20}O_2N_2$	79.88, 79.79	5.12, 5.21	7.09, 6.96	80.17	4.98	6.92
(XI)	4-$CH_3C_6H_4$	87	203.5—204	Benzene + methyl alcohol (4 : 1)	Red needles	$C_{27}H_{20}O_2N_2$	80.14, 80.02	4.83, 4.85	7.05, 6.99	80.17	4.98	6.92
(XII)	2,4-$(CH_3)_2C_6H_3$	91.5	173—174	Dioxane	Red needles	$C_{28}H_{22}O_2N_2$	80.40, 80.17	5.30, 5.47	6.73, 6.65	80.35	5.30	6.69
(XIII)	2,5-$(CH_3)_2C_6H_3$	93	185.5—186.5	Benzene + methyl alcohol (2 : 1)	Red plates	$C_{28}H_{22}O_2N_2$	80.56, 80.44	5.52, 5.40	6.70, 6.65	80.35	5.30	6.69
(XIV)	3,5-$(CH_3)_2C_6H_3$	92	176.5—176.7	Benzene + methyl alcohol (4 : 1)	Red broad needles	$C_{28}H_{22}O_2N_2$	80.55, 80.67	5.72, 5.55	6.99, 7.09	80.35	5.30	6.69

TABLE 3

Derivatives of Simple Ethers of 1-Amino-2-naphthol



R	Derivative	Molecular formula	Yield, %	Crystalline form	Melting point	Found %			Calc., %		
						C	H	N	C	H	N
C_2H_5	HCl-Salt	$C_{12}H_{14}ONCl$	65	Needles	223—225° (dec.)	—	—	6.01, 6.12	—	—	6.26
	N-benzoyl	$C_{19}H_{17}O_2N$		Needles	140.5—141.5	78.35, 78.18	5.97, 5.74	4.88	78.32	5.88	4.80
n-C_4H_9	HCl-Salt	$C_{14}H_{18}ONCl$	99.5	Needles	220—222 (dec.)	—	—	5.70, 5.59	—	—	5.56
	N-benzoyl	$C_{21}H_{21}O_2N$		Plates	115.5—116.7	79.16, 79.07	6.31, 6.48	4.22, 4.30	78.96	6.62	4.38
n-C_6H_{13}	HCl-Salt	$C_{16}H_{22}ONCl$	100	Needles	204—205 (dec.)	—	—	—	—	—	—
	N-benzoyl	$C_{23}H_{25}O_2N$		Plates	104.5—105.5	—	—	3.78, 3.97	—	—	4.03
n-C_8H_{17}	HCl-Salt	$C_{18}H_{26}ONCl$	93.5	Needles	177—179 (dec.)	—	—	—	—	—	—
	N-benzoyl	$C_{25}H_{29}O_2N$		Needles	95.5—96.5	79.60, 79.79	7.61, 7.51	3.77, 3.97	79.96	7.78	3.73
n-$C_{18}H_{37}$	HCl-Salt	$C_{28}H_{43}ONCl$	100	Needles	174—176 (dec.)	75.05, 75.16	10.25, 10.21	3.60	75.04	10.34	3.12
	N-benzoyl	$C_{35}H_{49}O_2N$		Plates	94.5—95.5	81.72, 81.83	9.58, 9.64	2.47, 2.63	81.50	9.57	2.71
$C_6H_5CH_2CH_2$	HCl-Salt	$C_{18}H_{18}ONCl$	88.5	Needles	193—195 (dec.)	—	—	—	—	—	—
	N-benzoyl	$C_{25}H_{21}O_2N$		Needles	131—131.7	—	—	3.68, 3.89	—	—	3.81
C_6H_5	HCl-Salt	$C_{16}H_{14}ONCl$	92.5	Needles	190—192 (dec.)	70.24, 70.29	5.22, 5.28	5.60, 5.48	70.71	5.19	5.15
	N-benzoyl	$C_{23}H_{17}O_2N$		Plates	171.8—172.5	80.94, 80.86	5.08, 4.98	4.27, 4.22	81.39	5.04	4.12
2-$CH_3C_6H_4$	HCl-Salt	$C_{17}H_{16}ONCl$	70	Needles	183.5—186.5 (dec.)	—	—	—	—	—	—
	N-benzoyl	$C_{24}H_{19}O_2N$		Plates	177.5—178.7	81.82, 81.36	5.26, 5.52	3.80, 3.78	81.56	5.41	3.96
4-$CH_3C_6H_4$	HCl-Salt	$C_{17}H_{16}ONCl$	93	Needles	231—233 (dec.)	71.41, 71.53	5.84, 6.05	5.08, 4.96	71.44	5.64	4.90
	N-benzoyl	$C_{24}H_{19}O_2N$		Needles	175—176	81.50, 81.44	5.64, 5.44	3.62, 3.81	81.56	5.41	3.96
3,5-$(CH_3)_2C_6H_3$	HCl-Salt	$C_{18}H_{18}ONCl$	53	Needles	180—183 (dec.)	—	—	—	—	—	—
	N-benzoyl	$C_{25}H_{21}O_2N$		Needles	179—179.6	81.60 81.56	5.45, 5.85	3.87, 3.92	81.71	5.76	3.81

removed by steam, the precipitate filtered off, washed with a 5% caustic soda solution to remove excess phenol, and then with boiling water. Further treatment of the precipitates was carried out as in the substitution of chlorine by alkoxygroups.

Yields, properties, and analytical data of 2-aroxy-2'-hydroxy-1,1'-azonaphthalenes (monoethers of 2,2'-dihydroxy-1,1'-azonaphthalene and aryl groups) are shown in Table 2. All monoethers listed in the table are highly soluble in the cold in chloroform and chlorobenzene (and, except for monoethers IX and XII, in benzene also), and poorly soluble in methyl and ethyl alcohols. Monoethers (IX) and (XIV) are highly soluble in toluene in the cold, (X), (XII), and (XIII) in dichloroethane. Monoether (IX) is poorly soluble in benzene in the cold, (IX), (X), (XII), and (XIV) in acetone, (IX), (XI), (XII), and (XIV) in acetic acid. Monoethers (X), (XII), and (XIII) are somewhat more highly soluble in the cold in carbon tetrachloride, (X) in pyridine, (XII) in dioxane, (XI) and (XIII) in acetone, (XIII) in acetic acid, (XII) in benzene and toluene. Monoethers (X), (XII), and (XIII) are highly soluble in acetone on heating, (IX) in benzene, (X) in pyridine and acetic acid, (XIII) in dioxane, (XII) less soluble in acetic acid, (IX) and (XII) in methyl and ethyl alcohols, (X) and (XIII) poorly soluble in methyl and ethyl alcohols.

Preparation of simple ethers of 1-amino-2-naphthol. 0.01 mole of the corresponding monoether of 2,2'-dihydroxy-1,1'-azonaphthalene (see above) was reduced by boiling with a solution of 9 g (0.04 mole) of stannous chloride in 100 ml of hydrochloric acid, then diluted with 100 ml of water, and the solution allowed to stand for 2-5 hr until clear. After cooling, the precipitate was filtered off and treated with 100 ml of 5% caustic soda solution (with the addition of 1 g of sodium hydrosulfite), and the 1-amino-2-alkoxy- (or aroxy)-naphthalene then extracted with ether several times (total volume of ether 50-70 ml). The ethereal layer separated out and was treated with 1 ml of concentrated hydrochloric acid, the precipitate of amine hydrochloride separating out was filtered off, dried spontaneously, recrystallized from methyl alcohol diluted to one-third full strength (in the case of the amine with an octadecoxy group—from the undiluted alcohol), and acidified with several drops of hydrochloric acid. The resulting amines were benzoylated by the Schotten-Baumann method, the N-benzoyl derivatives recrystallized from methyl alcohol (in the case of amines with ethoxy-, butoxy-, hexoxy-, octoxy- and phenylethoxy-groups, from the alcohol diluted to one-third full strength with water). Data on the hydrochlorides and N-benzoyl derivatives of simple ethers of 1-amino-2-naphthol are given in Table 3.

SUMMARY

1. By reacting 2-chloro-2'-hydroxy-1,1'-azonaphthalene with alcoholates and phenolates in the presence of a copper salt, a chlorine atom was substituted by the corresponding alkoxy- or aroxy- groups. 14 monoethers of 2,2'-dihydroxy-1,1'-azonaphthalene were obtained by this method.

2. By reduction cleavage of monoethers of 2,2'-dihydroxy-1,1'-azonaphthalene, 10 simple esters of 1-amino-2-naphthol were obtained.

3. The method for preparation of 1-amino-2-chloronaphthalene was described precisely.

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ESTERS OF ACETONE CYANOHYDRIN AND AROMATIC ACIDS

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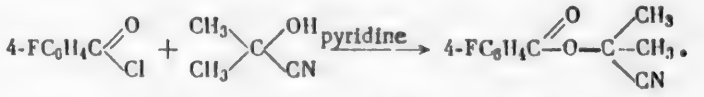
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2014-2016, June, 1960
Original article submitted June 2, 1959

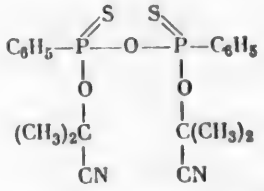
Acetone cyanohydrin is a freely available technical product. It has been used recently as a source of hydrocyanic acid in various addition reactions [1], in the preparation of cyanohydrins of other aldehydes and ketones [2], in the synthesis of nitriles from halogen derivatives [3], of esters of phosphorous and phosphoric acids [4], etc. Esters of acetone cyanohydrin and aromatic acids have received little study. Only the benzoic ester of acetone cyanohydrin has been obtained [5], and in low yield, it having an insecticidal action similar to that of the acetic ester, according to the patent cited [6].

With the idea of studying insecticidal properties, we prepared several esters of acetone cyanohydrin and aromatic carboxylic, sulfonic, and phosphinic acids, for instance, according to the scheme:

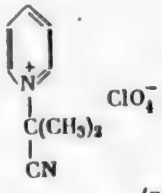


Esters of acetone cyanohydrin and 4-chloro-, 4-nitro-, 4-trifluoromethylbenzoic acids, phenyl- and 4-chlorophenylphosphinic acids, and 4-bromo, 4-methyl-, 2,5-dichloro-, and 4-nitrophenylsulfonic acids were prepared similarly.

On reacting the di-acid chloride of phenylthiophosphinic acid with acetone cyanohydrin, pyro-compound (A) was formed (according to the analytical data) instead of the diether.



(A)



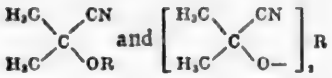
(B)

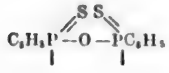
Recently it was shown that the esters of nitrobenzenesulfonic acids are strong alkylating agents [7]. It was of interest to investigate whether such a branched ester as that of acetone cyanohydrin and 4-nitrobenzenesulfonic acid would possess alkylating properties. It was found that this ester readily alkylates pyridine by heating on a water bath, with formation of a quaternary salt, which was isolated as the perchlorate (B).

Esters of 4-chloro-, 4-fluoro-, and 4-nitrobenzoic acids and acetone cyanohydrin possess some insecticidal properties.

EXPERIMENTAL

Esters of acetone cyanohydrin and aromatic acids were obtained in the following manner. To 0.02 mole of the acid chloride of the acid was added 0.02 mole of acetone cyanohydrin (in the case of dibasic phosphinic acids, 0.04 mole). The reaction was carried out with vigorous stirring in excess pyridine. For every 0.02 mole of the acid chloride of carboxylic acids, 3 ml of phosphinic and thiophosphinic acids was used –6 ml in the case of sulfonic acids–and 10 ml of pyridine. The acid chlorides of phosphinic, thiophosphinic, and sulfonic acids were dissolved in pyridine, acetone cyanohydrin added, and allowed to stand for 24 hr; in the case of carboxylic acids acetone cyanohydrin was mixed with pyridine and to it was gradually added the acid chloride of the acid (solid n-nitrobenzoylchloride was first dissolved in 50 ml of dry ether), and allowed to stand for 2 hr. The mixture was poured into water, the product washed free of pyridine, filtered off, dried, and crystallized. Data regarding the properties of the resulting esters of acetone cyanohydrin and analytic results are given in the table.

Esters of Acetone Cyanohydrin  and

R	% Yield.	Melting point	Solvent used in crystallization	Empirical formula	Analytical results: element	found, %	calc., %
4-$NO_2C_6H_4CO$–	73.2	124—125°	Benzene	$C_{11}H_{10}O_4N_2$	N	11.86, 11.95	11.96
4-ClC_6H_4CO–	71.5	63—64	Aqueous alcohol	$C_{11}H_{10}O_2NCl$	N	6.14, 5.96	6.26
4-FC_6H_4CO–	92.8	36—37	Petroleum ether	$C_{11}H_{10}O_2NF$	N	6.46, 6.58	6.76
4-$CF_3C_6H_4CO$–	72	65—66	Petroleum ether	$C_{12}H_{10}O_2NF_3$	N	5.43, 5.56	5.44
4-$NO_2C_6H_4SO_2$–	53.7	63.5—64.5	Aqueous alcohol	$C_{10}H_{10}O_5N_2S$	N	10.31, 10.18	10.37
2,5-$Cl_2C_6H_3SO_2$–	61.2	99.5—100.5	Aqueous alcohol	$C_{10}H_9O_3NSCl_2$	Cl	24.06, 24.20	24.14
4-$BrC_6H_4SO_2$–	50	92—93	Aqueous alcohol	$C_{10}H_{10}O_3NSBr$	Br	26.27, 26.26	26.31
4-$CH_3C_6H_4SO_2$–	60	97—98	Aqueous alcohol	$C_{11}H_{13}O_3NS$	S	13.32, 13.22	13.38
	70	72—73	Aqueous alcohol	$C_{11}H_{11}O_3N_2P$	N	9.76, 9.81	9.58
	54	76—77	Aqueous alcohol	$C_{11}H_{10}O_4N_2PCl$	N	8.28, 8.24	8.54
	21.5	107—108	Petroleum ether	$C_{20}H_{22}O_3N_2S_2P_2$	S	13.63, 13.78	13.79
					N	5.77, 5.79	6.03

All compounds shown in the table dissolve freely in alcohol, acetone, ether, dioxane, benzene (except the esters of p-nitrobenzoic acid and p-nitrobenzenesulfonic acid, which dissolve readily in acetone, ether, and dioxane, but in alcohol and benzene only on heating), with difficulty in petroleum ether, and are insoluble in water.

α-Cyanoisopropylpyridine perchlorate. 0.3 g of the α-cyanoisopropyl ester of 4-nitrobenzenesulfonic acid and 0.5 g of pyridine were heated on a water bath for 30 min. The mixture was washed with ether; 0.36 g (94.7%) of quaternary salt was obtained. It was dissolved in water and the perchlorate precipitated using sodium perchlorate. M.p. 191-192°C (from alcohol).

Found %: N 11.49, 11.55. $C_9H_{11}O_4N_2Cl$. Calculated %: N 11.35.

SUMMARY

Esters of acetone cyanohydrin and 4-fluoro-, 4-chloro-, 4-nitro-, 4-trifluoromethylbenzoic acids, phenyl- and 4-chlorophenylphosphinic acids, and 4-bromo-, 4-methyl-, 2,5-dichloro- and 4-nitrophenylsulfonic acids were obtained.

It was shown that the α-cyanoisopropyl ester of 4-nitrobenzenesulfonic acid possesses alkylating properties.

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•Original Russian pagination. See C. B. translation.

THE SYNTHESIS OF α,β-UNSATURATED KETONES OF THE FURAN SERIES AND STUDY OF THEIR TRANSFORMATIONS

III. CONDENSATION OF 5-NITROFURFUROL WITH METHYL KETONES

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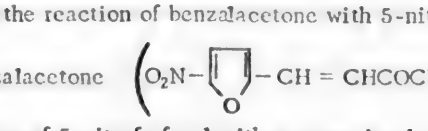
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2017-2021,
June, 1960
Original article submitted June 7, 1959

α,β-Unsaturated ketones which contain aromatic heterocyclic radicals have attracted much interest because of their physiological activity and the possibility of their use for further synthesis. In this respect there can be great interest in the still almost unknown α,β-unsaturated ketones of the furan series which contain a halogen or a nitro group in position 5, for these substituents not only increase the stability of the furan ring, but also increase its bacteriostatic properties.

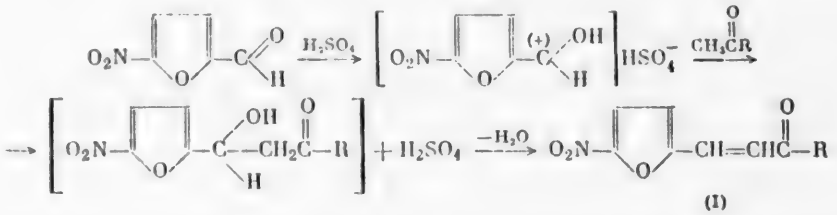
We have previously shown that condensation of 5-halofurfurols with acetone [1] and acetophenone [2] occurs only in an alkaline medium. Independent of the ratio of starting components the condensation of 5-halofurfurols with acetone results in di-(5-halofurfurylidene)-acetone with yields of more than 90%, while in the case of unsubstituted furfurols, depending on the ratio of reagents, we may obtain the monofurfurylidene- or the difurfurylideneacetone [3]. In the condensation of 5-halofurfurol with methyl ketones CH_3COR, if R is C_6H_5 [2], the difurfurylidene derivative is excluded because of R, but in this case a saturated diketone is formed because of addition of a second molecule of $CH_3COC_6H_5$ to the double bond of the α,β-unsaturated ketone.

The presence of a nitro group in furfurol activates still more the hydrogen of the CH_3 group. Also, the presence of an electrophilic group makes the 5-nitrofurfurol more active compared to furfurol in reactions of nucleophilic addition on the carbonyl group, since it permits an increase in the partial positive charge on the carbonyl carbon. Actually, in the condensation of 5-nitrofurfurol with acetone, just as in the case of condensation with 5-halofurfurol, di-(5-nitrofurfurylidene)-acetone is formed [4]. However, the condensation of nitrofurfurol with acetone occurs in an acid medium (H_2SO_4). In an alkaline medium, nitrofurfurol easily changes, forming a dark, amorphous precipitate of an unexplained nature. We have succeeded in increasing the yield of di-(5-nitrofurfurylidene)-acetone in an acid medium from 34% as given in the literature [4] to 57%. We have prepared its 2,4-dinitrophenylhydrazone and semicarbazone.

We have tried to obtain mono-5-nitrofurfurylideneacetone by the reaction of replacing benzaldehyde from benzalacetone with 5-nitrofurfurol by boiling in an aqueous medium in the presence of mineral acids, by analogy with the reaction of replacing benzaldehyde by 5-nitrofurfurol from 3-benzylideneamino-2-oxazolidone [5]. The attempt to displace benzaldehyde by 5-nitrofurfurol from di-(benzal)-acetone under the same conditions did not succeed. In the reaction of benzalacetone with 5-nitrofurfurol we isolated the condensation product 5-nitrofurfurylidenebenzalacetone  which was also obtained under conditions of condensation of 5-nitrofurfurol with acetone in glacial acetic acid [6]. We obtained its 2,4-dinitrophenylhydrazone.

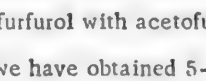
We studied further the reaction of condensation of 5-nitrofurfurol with acetophenone and acetofuran. The condensation of 5-nitrofurfurol with acetophenone goes most smoothly in the presence of sulfuric acid. Here, in distinction from the 5-halofurfurols [2], independent of the ratio of reagents and reaction conditions we get only one product, mono-5-nitrofurfurylideneacetophenone (I, R = C_6H_5) with a 75% yield. We did not succeed in attempts to add a molecule of acetophenone to 5-nitrofurfurylideneacetophenone.

In contradiction to the 5-halofurfurylideneacetophenones, 5-nitrofurfurylideneacetophenone easily forms derivatives at the carbonyl group. Thus, we succeeded in obtaining not only the 2,4-dinitrophenylhydrazone of 5-nitrofurfurylideneacetophenone, but also the oxime and semicarbazone.



(I)

5-Nitrofurfurylideneacetophenone can be obtained by the reaction of exchange of bromine by the NO_2 group in 5-bromofurfurylideneacetophenone by heating the latter with $AgNO_2$ in glacial acetic acid in the sunlight.

The condensation of 5-nitrofurfurol with acetofuran is accompanied by partial tarring due to the acidophobic nature of acetofuran. Here we have obtained 5-nitrofurfurylideneacetofuran  and its 2,4-dinitrophenylhydrazone.

The compounds which we obtained were studied in the microbiology department of the Rostov State Medical Institute, for bacteriocidal action with respect to microbes. Experiments showed that 5-nitrofurfurylideneacetophenone and 5-nitrofurfurylideneacetofuran have strong bacteriocidal action and inhibit the growth of microbes (anthrax bacteria, dysentery bacteria, Staphylococcus aureus) in dilutions of 1 : 50,000. 5-Nitrofurfurylideneacetophenone is more active than 5-nitrofurfurylideneacetofuran.

EXPERIMENTAL

Di-(5-nitrofurfurylidene)-acetone. a) We dissolved 2.82 g of 5-nitrofurfurol in 10 ml of glacial acetic acid and then added 0.7 g of acetone dropwise. The reaction mass was cooled with ice and 1.4 ml of concentrated H_2SO_4 (d 1.82) was added by drops. The mixture was allowed to stand in the sun. After five hours dark crystals separated from the intensely colored solution. The mixture was poured into ice water. The brown precipitate was separated and washed with water to remove acetic acid. Yield 1.12 g (36.8%). After two recrystallizations from acetic acid, m.p. 184-185°.

b) We dissolved 4.4 g of 5-nitrofurfurol diacetate in 9 ml of glacial acetic acid, in the presence of 0.6 ml of concentrated sulfuric acid. The resulting solution was heated with shaking for 5-7 min on a boiling water bath, then cooled to 0° and to the cooled solution we added dropwise an equimolar amount of acetone (1.4 ml), then by drops and with mechanical stirring, 1 ml of concentrated sulfuric acid. The reaction mass was stirred for two hours and stood overnight, after which it was poured into ice water; the precipitate was washed with water. Yield 1.6 g (57%). After two recrystallizations from acetic acid, m.p. 184-185°, from CCl_4, m.p. 197°.

Found %: N 9.10, 9.17. $C_{13}H_8O_7N_2$. Calculated %: N 9.21.

2,4-Dinitrophenylhydrazone of di-(5-nitrofurfurylidene)-acetone [7] was obtained from 0.2 g of ketone with m.p. 184-185° in 5 ml of alcohol and 5 ml of a hot solution of 1 g of 2,4-dinitrophenylhydrazine, 5 ml of concentrated hydrochloric acid, 5 ml of water, and 40 ml of ethanol, with ten minutes heating. The precipitate was washed with hot dilute hydrochloric acid and then with water to remove residual acid (to Congo). Yield 66%, m.p. 221-222°.

Found %: N 16.25, 16.61. $C_{19}H_{12}O_{10}N_6 \cdot H_2O$. Calculated %: N 16.16.

5-Nitrofurfurylidenebenzalacetone. To a solution of 5.64 g of 5- nitrofurfurol and 2.92 g of benzalacetone in glacial acetic acid was added dropwise 0.46 ml of concentrated H_2SO_4. The mixture stood for a day and then the intensely colored solution was poured into 100 ml of alcohol. Fine crystals precipitated, after separation of which the rest of the product was separated from the mother liquor by dilution with water. Total yield 2.22 g (41.2%). Recrystallization from methanol and water in different ratios gave pale yellow crystals with m.p. 124-125°.

Found %: N 5.11, 5.28. $C_{15}H_{11}O_4N$. Calculated %: N 5.24.

2,4-Dinitrophenylhydrazone of 5-nitrofurfurylidenebenzalacetone was obtained similarly to the preceding [7]. From 0.08 g of the ketone we obtained 0.1 g (83%) of the 2,4-dinitrophenylhydrazone, m.p. 223-224°.

Found %: N 15.87, 15.66. $C_{21}H_{15}O_7N_5$. Calculated %: N 15.58.

5-Nitrofurfurylideneacetophenone. a) Obtained like di-(5-nitrofurfurylidene)-acetone. Yield 2.27 g (46.5%), m.p. 137-138°; recrystallization from acetic acid did not raise the m.p.

Found %: N 5.84, 5.67. $C_{13}H_9O_4N$. Calculated %: N 5.75.

b) To 12.16 g of 5-nitrofurfurol diacetate in 25 ml of glacial acetic acid was added 1.3 ml of concentrated H_2SO_4 dropwise with shaking. The mixture was heated on a boiling water bath for 5-7 min, then cooled to 0°. To the resulting solution of 5-nitrofurfurol in acetic acid was added 5.8 ml of acetophenone, and then 3 ml of concentrated H_2SO_4, dropwise with shaking. After 3.5 hr standing in clear sunlight crystals of 5-nitrofurfurylideneacetophenone precipitated. Yield 8.95 g (74.6%), m.p. 137.5° (from acetic acid), light brown crystals.

2,4-Dinitrophenylhydrazone of 5-nitrofurfurylideneacetophenone were obtained as before. Yield 94%. m.p. 254-255° (from nitrobenzene).

Found %: N 16.02, 16.03. $C_{19}H_{13}O_7N_5$. Calculated %: N 16.54,

c) A mixture of 1.38 g of 5-bromofurfurylideneacetophenone, 3.08 g of $AgNO_2$, and 20 ml of glacial acetic acid stood for a day, then was boiled for one hour with illumination by sunlight, filtered hot and the filtrate diluted with water. The precipitate was washed with acetic acid. Yield 0.4 g (33%), m.p. 137-138° (from acetic acid).

The oxime of 5-nitrofurfurylideneacetophenone was obtained by heating a solution of the ketone in 30 ml of alcohol and a saturated solution of hydroxylamine hydrochloride in 60% alcohol for two hours, then allowing the reaction mass to stand overnight. After addition of a solution of sodium carbonate (1 g) in 30 ml of water the oxime precipitated as yellow crystals. Yield 90%, m.p. 118-119° (from alcohol-water solution).

Found %: N 10.64, 10.67 $C_{13}H_{10}O_4N_2$. Calculated %: N 10.84.

The semicarbazone of 5-nitrofurfurylideneacetophenone was obtained by heating a solution of 1 g of the ketone in 30 ml of alcohol, a saturated solution of 1 g of semicarbazide hydrochloride and 1 g of sodium acetate in water; after 10 min, crystals precipitated. Yield 42%, m.p. 214° (from acetic acid), yellow plates.

Found %: N 18.61, 18.64. $C_{14}H_{12}O_4N_4$. Calculated %: N 18.66.

The thiosemicarbazone of 5-nitrofurfurylideneacetophenone was obtained in a similar way (without sodium acetate). Orange crystals. Yield 94%, m.p. 207° (from dichloroethane).

Found %: N 17.74, 17.68. $C_{14}H_{12}O_3N_4S$. Calculated %: N 17.70.

5-Nitrofurfurylideneacetofuran. a) A mixture of 0.7 g of 5-nitrofurfurol and 0.55 g of acetofuran was dissolved in 5 ml of glacial acetic acid and to the solution with slight cooling was added dropwise 0.29 ml of concentrated H_2SO_4; the mixture stood for 1.5 days. Then the intensely colored solution was poured onto ice with strong stirring. Yield of unpurified product 0.35 g (30%), m.p. 178-179° (from acetic acid).

b) We dissolved 1.21 g of the diacetate of 5-nitrofurfurol in 5 ml of glacial acetic acid in the presence of 0.015 ml of concentrated H_2SO_4. The solution was heated on the boiling water bath for 5-7 min; cooled to 0°.

To the cooled solution was added 0.55 g of acetofuran and after solution of the latter, 0.3 ml of concentrated H_2SO_4 was added dropwise. The reaction mixture stood for two days and then was poured onto ice with stirring. Yield 0.2 g (17%), m.p. 162-164°. After crystallization from acetic acid, m.p. 178-179°.

Found %: N 5.94, 6.02. $C_{10}H_7O_4N$. Calculated %: N 6.07.

The 2,4-dinitrophenylhydrazone of 5-nitrofurfurylideneacetofuran was obtained as described. Yield 70% m.p. 225-226° (from acetic acid).

Found %: N 16.87, 16.78. $C_{17}H_{11}O_8N_5$. Calculated %: N 16.94.

SUMMARY

1. We have established that in an acid medium (H_2SO_4) 5-nitrofurfurol undergoes a condensation reaction with methyl ketones (acetophenone, acetofuran). We have obtained 5-nitrofurfurylideneacetophenone, 5-nitrofurfurylideneacetofuran, and their derivatives.

2. We have shown that 5-nitrofurfurol does not replace benzaldehyde from benzalacetone, but reacts with the latter in a condensation, forming 5-nitrofurfurylidenebenzalacetone.

3. We have improved the method of synthesis of bis-5-nitrofurfurylideneacetone described in the literature, reaching a yield of 57%.

4. We have shown the possibility of exchange of bromine in 5-bromofurfurylideneacetophenone with the nitro group by heating with $AgNO_2$ in glacial acetic acid with illumination by sunlight.

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STUDIES IN THE FIELD OF SYNTHESIS AND REACTIONS IN THE DIARYLUREA SERIES

X. STUDY OF THE REACTION OF PHOSGENATION OF 2,4,5-TRICHLOROANILINE UNDER THE CONDITIONS OF FORMATION OF 2,2',4,4',5,5'-HEXACHLORODIPHENYLUREA

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2021-2024, June, 1960
Original article submitted June 3, 1959

We have showed in a number of studies [1, 2] that the rate of the reaction of phosgenation of aromatic amines is affected by temperature conditions, phase state of contacting systems, and removal of hydrogen chloride from the sphere of the reaction. We also showed that the rate of reaction under given conditions [2] depends on the nucleophilic properties of the aromatic amines, which in turn depend on the number and nature of the substituents in the aromatic ring. Aromatic amines with low nucleophilic properties react with phosgene with great difficulty. In this case, in order to obtain diarylureas with practical yields, the reaction is carried out in organic solvents at higher temperatures, and sometimes under pressure. Aromatic amines which have high nucleophilic properties react easily with phosgene, and the yields of diarylureas are almost quantitative. The results obtained in our work [1, 2] are given in Table 1.

TABLE 1

Amines	Conditions of phosgenation	Yield of diarylureas, %
$C_6H_5NH_2$	A 20°	99.4
2-$CH_3OC_6H_4NH_2$	A 25	98.8
4-$CH_3OC_6H_4NH_2$	B 40	94.1
2-$CH_3C_6H_4NH_2$	B 40	95.2
2-$NO_2C_6H_4NH_2$	C 100	80.8
3-$NO_2C_6H_4NH_2$	B 40	79.5
4-$NO_2C_6H_4NH_2$	B 40	91.5
2-CH_3-4-$NO_2C_6H_3NH_2$	B 40	79.6
2-$ClC_6H_4NH_2$	A 30	87.6
3-$ClC_6H_4NH_2$	A 30	85.3
4-$ClC_6H_4NH_2$	A 30	92.5
2,4-$Cl_2C_6H_3NH_2$	B 120	90.5
2,4, 6-$Cl_3C_6H_2NH_2$	B 130	86.3

Designations in table: A—aqueous alkali medium; B—nitrobenzene solvent; C—toluene solvent.

In addition, the rate of reaction of phosgenation of aromatic amines depends on steric factors and also on the solubility of the amines in water and in organic solvents [3].

In the present work we have studied the phosgenation of 2,4,5-trichloroaniline, that is, an aromatic amine with low nucleophilic properties because of the presence in the ring of three electronegative substituents. The reaction was carried out in an aqueous medium and in a medium of organic solvent. When trichloroaniline was phosgenated in a water medium, the experiments were carried out in the presence of soda and in an acid medium. When we phosgenated in an acid medium, the maximum yield of hexachlorodiphenylurea was 94%. However, when we used soda, the yield of hexachlorodiphenylurea was markedly less (78%) which is explained by the hydrolysis of phosgene in an alkaline medium. We showed that the rate of the phosgenation reaction in water also depends on the accumulation in the reaction mass of hydrochloric acid and hexachlorodiphenylurea.

TABLE 2

Medium	Amt. of phosgene, % of theory	Yield of hexachlorodiphenylurea, %	M.p. of product
Dichloroethane + water	300	94.73	302°
Dichloroethane + aqueous soda solution	300	99.8	303
The same	200	99.8	302

TABLE 3

Organic solvent	Yield of hexachlorodiphenylurea, %	M.p. of product
Dichloroethane	78.5	303°
1st mother liquor	89.4	302.5
2nd mother liquor	96.6	303
3rd mother liquor	98.1	302
4th mother liquor	129.0	302

At the beginning of the process a considerable part of the phosgene is hydrolyzed. Then, when the amount of accumulated hydrochloric acid reaches about 5%, the phosgenation process begins to go more intensively, but then, when the concentration of acid rises to 15%, the rate of the reaction of phosgene with trichloroaniline falls.

Since the solubility of trichloroaniline in water is very slight, in order to supply homogeneous conditions and get pure hexachlorodiphenylurea, we carried out the process of phosgenation in a medium of organic solvent. For this purpose we used as solvents dichloroethane, chlorobenzene, and xylene. We showed that the phosgenation reaction in media of these solvents at temperatures of their boiling points did not go to completion. Considerable amounts (up to 30%) of trichloroaniline hydrochloride remained in the final product. Carrying out these reactions under conditions favorable for the phosgenation of 2,4,6-trichloroaniline [3] resulted in low yields of hexachlorodiphenylurea and tarring. The best results were obtained in the phosgenation of trichloroaniline in a medium of dichloroethane–water at 25°. Under these conditions the yield of hexachlorodiphenylurea reached quantitative. However, at this temperature obtaining the hexachlorodiphenylurea was accompanied by formation of appreciable amounts of trichloroaniline hydrochloride. In this connection, we undertook experiments to select the optimum conditions for running this reaction at 25° which would prevent the formation of trichloroaniline hydrochloride. We succeeded in finding such conditions, running the process in a water–dichloroethane medium in the presence of calcined soda. Then the starting trichloroaniline and the phosgene placed in the reactor were in the dichloroethane solution. The reaction thus took place under homogeneous conditions; the presence of water completely prevented the possibility of formation of, and contamination of the final product by, trichloroaniline hydrochloride. The addition of some calcined soda to the reaction medium permitted an increased yield of hexachlorodiphenylurea. A positive effect on the course of the process was also shown by addition to the reaction mass before phosgenation of a small amount of the emulsifier OP-7.

When the phosgenation of 2,4,5-trichloroaniline was carried out under optimum conditions, most of the hexachlorodiphenylurea precipitated and was separated by filtration. The mother liquor was used for the next phosgenation. The total yield of 2,2',4,4',5,5'- hexachlorodiphenylurea was 98.3% of the theoretical; the product was a white powder which did not contain contaminants.

EXPERIMENTAL

1. Phosgenation of 2,4,5-trichloroaniline in aqueous medium. In a reactor fitted with a stirrer, thermometer, outlet tube, and bubbler, was placed 42 g of 2,4,5-trichloroaniline, 200 ml of water solution of soda (110% of the theoretical) and several drops of emulsifier OP-7. With energetic stirring during four hours at 100° we introduced 200% of the theoretical of phosgene. The hexachlorodiphenylurea which precipitated was filtered off and washed on the filter with hot water. Yield 78.2%, m.p. 302°.

Found %: N 6.32, 6.54; Cl 50.41, 50.72. $C_{13}H_6ON_2Cl_6$. Calculated %: N 6.68.

In another experiment the yield of hexachlorodiphenylurea was 94%, m.p. 303° [3].

2. Phosgenation of 2,4,5-trichloroaniline in dichloroethane, chlorobenzene, and xylene. The experiments were carried out in the same reactor at ratios of trichloroaniline to solvent of 1 : 4 (by weight). Phosgenation was carried out for three hours with addition of 300% of the theoretical of phosgene. The yields of hexachlorodiphenylurea were: in dichloroethane at 25°, 73.5%; in chlorobenzene at 120°, 63.8%; and in xylene at 120°, 64.3%. In all cases the hexachlorodiphenylurea had m.p. 302-303°.

3. Phosgenation of 2,4,5-trichloroaniline in a water-dichloroethane medium. In all the experiments the ratio of components used was: trichloroaniline 1 weight part, dichloroethane 4 parts by volume, water or a 15-20% soda solution 4 parts. The reaction was carried out at 25° for four hours. Results are given in Table 2.

For the best and most economical use of the solvent, we used the mother liquors of dichloroethane from previous runs in later operations, adding to them a 20% aqueous soda solution. In all these operations the amount of phosgene was 200% of the theory. Results are given in Table 3.

It is clear from these results that in running five operations, the total yield of hexachlorodiphenylurea is 98.3%.

SUMMARY

1. We have studied the reaction of phosgenation of 2,4,5-trichloroaniline in water, in organic solvents, and in water-dichloroethane.

2. We have found the optimum reaction conditions for phosgenation of 2,4,5-trichloroaniline to be in water-dichloroethane, with a yield of very pure 2,2',4,4',5,5'-hexachlorodiphenylurea of not less than 98%.

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•Original Russian pagination. See C. B. translation.

STUDIES IN THE FIELD OF SYNTHESIS AND REACTIONS IN THE DIARYLUREA SERIES

XI. STUDY OF THE MECHANISM OF REACTION OF 2,4,5-TRICHLOROANILINE WITH PHOSGENE

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2024-2027, June, 1960
Original article submitted June 3, 1959

Problems connected with the mechanism of reaction of amines with phosgene have been little considered in the literature. Some authors [1] assume that the phosgenation of various amines begins with the addition of two molecules of amine to one molecule of phosgene. However the question remains completely open so far as concerns the direction and mechanism of reaction of phosgene with anilines substituted in the ring by halogens. This fact led us to investigate the reaction of 2,4,5-trichloroaniline with phosgene, and also the reactions of 2,4,5-trichlorophenylcarbamyl chloride and 2,4,5-trichlorophenyl isocyanate with 2,4,5-trichloroaniline under the conditions of formation of 2,2',4,4',5,5'-hexachlorodiphenylurea. Study of these reactions was carried out at different molar ratios of reacting components in a medium of anhydrous dichloroethane, since in water or in the presence of water, reactions of this type go with particularly great speed [2].

At a mole ratio of phosgene to trichloroaniline of 1 : 2 the yield of hexachlorodiphenylurea is only 37.7% and along with this there is obtained a large amount (56.4%) of trichloroaniline hydrochloride and some (5.6%) trichlorophenylcarbamyl chloride; trichlorophenyl isocyanate is not found. The formation of a large amount of trichloroaniline hydrochloride is thus explained: the hydrogen chloride evolved as a result of the reaction reacts quickly with the still free starting amine to form its hydrochloride. As a result of this, part of the trichlorophenylcarbamyl chloride does not react, since under these conditions it cannot react with trichloroaniline hydrochloride. Carrying out the reaction under the same conditions in the presence of a hydrogen chloride acceptor (soda) leads to an increased yield of hexachlorodiphenylurea to 50%. Along with this there is formed a considerable amount (30.5%) of trichlorophenyl isocyanate; only 8.7% trichloroaniline hydrochloride is found and trichlorophenylcarbamyl chloride does not appear at all. In this case the soda not only combines with the hydrochloric acid formed in the reaction, but also permits splitting of the latter from trichlorophenylcarbamyl chloride and formation of trichlorophenyl isocyanate.

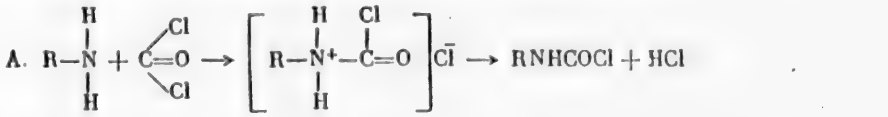
However, at mole ratios of phosgene to trichloroaniline of 1 : 4, in the absence of soda, the yield of hexachlorodiphenylurea reaches 53%. Then a large amount of trichloroaniline hydrochloride (45%) is formed; trichlorophenyl isocyanate is not observed. Formation of a large amount of trichloroaniline hydrochloride is thus explained: the excess amine plays the role of a hydrogen chloride acceptor.

We previously [3] synthesized trichlorophenylcarbamyl chloride and trichlorophenyl isocyanate, and in the present work we have studied the conditions of forming these intermediates in the phosgenation of trichloroaniline and their reaction with trichloroaniline. Considering that arylcarbamyl chlorides and aryl isocyanates are very reactive compounds [4], we carried out the reaction of these substances with trichloroaniline at low temperatures.

In the reaction of trichlorophenylcarbamyl chloride with trichloroaniline there is much value in the removal from the reaction sphere of the hydrogen chloride, using various acceptors. Thus, for example, at mole ratios of reacting substances of 1 : 1 in the absence of soda, the yield of hexachlorodiphenylurea is 33.5%, while the yield of trichloroaniline hydrochloride is 46.3%, and a considerable part of the trichloroaniline does not react. An entirely different result is obtained in the presence of soda where the yield of hexachlorodiphenylurea is 93.5%, and only 2.8% trichloroaniline hydrochloride is formed. However, when this reaction is carried out in the absence of soda, but with a mole ratio of trichloroaniline to trichlorophenylcarbamyl chloride of 2 : 1, the yield of hexachlorodiphenylurea is 98.2% and a large quantity (47.2%) of trichloroaniline hydrochloride is obtained. Only 3.6% of trichlorophenylcarbamyl chloride appears. This result is not unexpected: in this case the excess trichloroaniline plays the part of the hydrogen chloride acceptor.

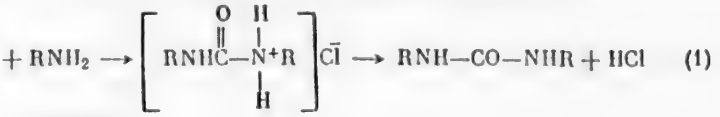
In the reaction of trichlorophenyl isocyanate with trichloroaniline at mole ratios of reacting components of 1 : 1, the yield of hexachlorodiphenylurea is almost quantitative.

Thus, as a result of this study we have shown that in the phosgenation of trichloroaniline, trichlorophenylcarbamyl chloride and trichlorophenyl isocyanate are formed as intermediates. On the basis of these results the mechanism of the phosgenation of trichloroaniline can be represented by scheme 1.



A. $R-\overset{H}{\underset{H}{N}} + C(=O)(Cl)(Cl) \rightarrow \left[R-\overset{H}{\underset{H}{N^+}}-C(Cl)=O\right]\bar{Cl} \rightarrow RNHCOCl + HCl$

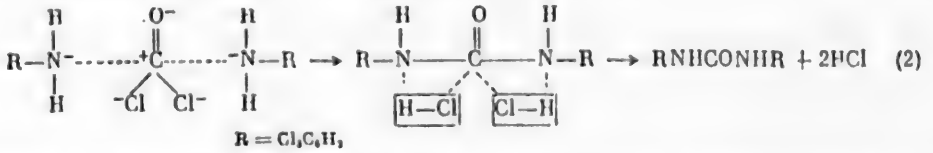
B. a) $RNHCOCl \rightarrow RNCO + HCl$, $RNCO + RNH_2 \rightarrow RNHCONHR$;



b) $RNHCOCl + RNH_2 \rightarrow \left[RNHC(=O)-\overset{H}{\underset{H}{N^+}}R\right]\bar{Cl} \rightarrow RNH-CO-NHR + HCl$ (1)

$R = C_6H_3Cl_2$

Along with this, considering the very electrophilic character of phosgene, we also think it is possible that two molecules of aromatic amine add to a phosgene molecule followed by splitting of two molecules of hydrogen chloride and formation of the diarylurea by scheme 2.



$R-\overset{H}{\underset{H}{N}}\cdots\cdots C(=O^-)\cdots\cdots\overset{H}{\underset{H}{N}}-R \rightarrow R-N(H)-C(=O)-N(H)-R \rightarrow RNHCONHR + 2HCl$ (2)

$R = Cl_3C_6H_2$

However, this mechanism of the process is evidently more suitable in the phosgenation of aromatic amines with higher nucleophilic properties.

Hence, it seems likely that the process which takes place in the phosgenation of aromatic amines begins with formation of products of addition of the amines to phosgene. After this there is the further very complex transformation which was described in our study [2].

EXPERIMENTAL

Reaction of 2,4,5-trichloroaniline with phosgene. Separation of the reaction products was based on their properties: 2,4,5-trichlorophenylcarbamyl chloride contains a mobile chlorine and dissolves easily in dichloroethane; 2,4,5 trichloroaniline hydrochloride also contains mobile chlorine, but does not dissolve at all in dichloroethane; 2,4,5-trichlorophenyl isocyanate is easily soluble in dichloroethane, but does not contain mobile chlorine; 2,2',4,4',5,5'-hexachlorodiphenylurea does not contain mobile chlorine and is poorly soluble in dichloroethane.

We dissolved 0.07 mole of 2,4,5-trichloroaniline in 50 ml of dichloroethane and with energetic stirring at 20° passed in different amounts of phosgene (0.0175, 0.035, and 0.07 mole) in the course of 100 min. In some cases the reaction was carried out in the presence of soda. The precipitate which formed consisted of a

Amt. of reacting components	Obtained in the reaction, %			
	hexachlorodiphenyl	trichloroaniline hydrochloride	trichlorophenylcarbamyl chloride	trichlorophenyl isocyanate
Reaction of 2,4,5-trichloroaniline (I) with phosgene (II)				
3.5 g (II), 6.67 g (I). Mole ratio 1 : 1	45.0	37.6	None	17.0
3.5 g (II), 13.74 g (I) (1 : 2)	37.7	56.4	5.6	None
3.5 g (II), 13.74 g (I), 3.7 g soda (1 : 2 : 1)	50.0	8.7	None	30.5
1.75 g (II), 13.74 g (I) (1 : 4)	53.8	45.0	None	None
Reaction of 2,4,5-trichlorophenylcarbamyl chloride (III) with 2,4,5-trichloroaniline (I)				
9.06 g (III), 6.68 g (I) (1 : 1)	33.5	46.3	48.0	None
9.06 g (III), 6.87 g (I), 3.71 g dry soda (1 : 1 : 1)	93.5	2.8	None	None
9.06 g (III), 13.74 g (I) (1 : 2)	98.2	47.2	3.6	None
Reaction of 2,4,5-trichlorophenyl isocyanate (IV) with 2,4,5-trichloroaniline (I)				
7.8 g (IV), 6.87 g (I) (1 : 1)	98.5	None	None	None

mixture of hexachlorodiphenylurea and trichloroaniline hydrochloride, and the dichloroethane solution contained trichlorophenylcarbamyl chloride and trichlorophenyl isocyanate. The amount of the components which formed was determined as follows.

a) Hexachlorodiphenylurea. The precipitate which formed in this reaction was filtered off, washed with dichloroethane, and dried. The dichloroethane solution was kept with the wash dichloroethane. For destruction of the trichloroaniline hydrochloride and for separation of the base the trichloroaniline precipitate was treated with soda and filtered, washed with water, and carefully pressed out on filter paper, after which it was treated with alcohol (the alcohol solution was kept), dried, and weighed and its melting point determined.

b) Trichloroaniline hydrochloride. The alcohol solution was evaporated dry, the residue was weighed and the melting point of the trichloroaniline base was determined.

c) Trichlorophenylcarbamyl chloride. The dichloroethane solution was evaporated dry and weighed. A sample of the precipitate was treated with 0.5 N sodium hydroxide, heated 15 min under reflux, and the mobile chlorine was determined by the Volhard method with calculation of the amount of trichlorophenylcarbamyl chloride.

d) Trichlorophenyl isocyanate was determined in the precipitate after evaporation of the alcohol, by difference between the total amount of precipitate and the amount of trichlorophenylcarbamyl chloride found. The results of the experiments are given in the table.

Reaction of 2,4,5-trichlorophenylcarbamyl chloride with 2,4,5-trichloroaniline. We dissolved 0.035 mole of 2,4,5-trichlorophenylcarbamyl chloride in 50 ml of dry dichloroethane. To the solution we added 0.035 mole of 2,4,5-trichloroaniline. (In some cases the reaction was carried out in the presence of 0.035 mole of dry soda). The reaction took two hours at 20°. The resulting product was treated as described. The results are given in the table.

Reaction of 2,4,5-trichlorophenyl isocyanate with 2,4,5-trichloroaniline. We dissolved 0.035 mole of 2,4,5-trichlorophenyl isocyanate in 25 ml of dry dichloroethane and to the solution added 0.035 mole of 2,4,5-trichloroaniline; the mixture was stirred for two hours at 20°. Separation of the products was carried out by the described method. Results of the experiments are given in the table.

SUMMARY

1. We have established that in preparing hexachlorodiphenylurea by phosgenation of trichloroaniline, there are formed as intermediate products trichlorophenylcarbamyl chloride and trichlorophenyl isocyanate. We have studied the reaction of these compounds with trichloroaniline.

2. We have shown the role of hydrogen chloride in the phosgenation of trichloroaniline and in the reaction of trichlorophenylcarbamyl chloride with trichloroaniline.

3. We have given the mechanism of the phosgenation of trichloroaniline in the formation of hexachlorodiphenylurea.

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REACTIONS OF MAGNESYL AMINES

VII. SYNTHESIS AND PROPERTIES OF ARYL (ALKYL) AMIDES OF ANTHRANILIC ACID

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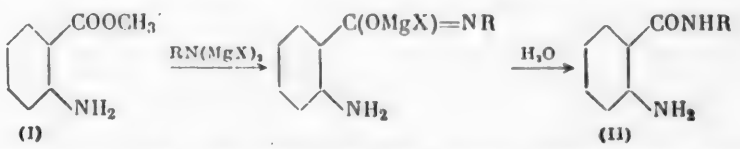
Translated from Zhurnal Obshchei, Khimii, Vol. 30, No. 6, pp. 2028-2030, June, 1960
Original article submitted June 4, 1959

Aryl (alkyl) amides of anthranilic acid are of interest as starting compounds for the synthesis of heterocyclic compounds: derivatives of acridine [1], phenanthridine [2], quinazolone [3], and benzo-1,2,3-triazine [4]. Some amide compounds of anthranilic acid are active biologically [5]. However, the methods of containing them cannot be considered properly worked out. They are usually obtained by reaction between o-nitrobenzoyl chloride and amines, with later reduction of the nitro group [6], by the action of amines on the anhydride of isatoic acid [7], and by heating aryl amides of phosphorous acid with anthranilic acid [8]. According to the method of [7], along with the aryl amides of anthranilic acid there are formed ω-aryl-o-uramidobenzoic acid or products of its condensation [9]; according to method [8] the yield does not exceed 20-22%.

We have set ourselves the problem of working out a method for preparing aryl (alkyl) amides of anthranilic acid (II) based on methyl anthranilate (I) and magnesyl amines according to the following scheme:



(I) (II)

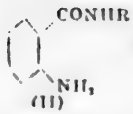
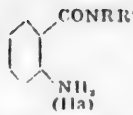
Experiments showed that the highest yields of (II) are obtained when 2 moles of dimagnesyl amine are taken per 1 mole of (I). The excess of magnesyl amine is necessary because (I) contains mobile hydrogen atoms (the hydrogen of the NH_2 group). In the reaction we used primary and secondary aliphatic, aromatic, and aliphatic-aromatic amines.

The results of the experiments are given in the table. This shows that aryl amides of anthranilic acid are obtained in yields of 49-99%. An exception is the mesidide of anthranilic acid (Expt. 10) whose small yield is probably explained by steric hindrance which can appear in the N,N-bis(bromomagnesium)-mesidine.

Aryl (alkyl) amides of anthranilic acid are colorless, crystalline substances, soluble in the usual organic solvents and in mineral acids.

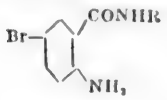
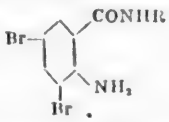
EXPERIMENTAL

Anthranilic acid anilide (Expt. 1). To ethyl magnesium iodide obtained from 62.4 g of ethyl iodide and 9.6 g of magnesium in 180 ml of ether was added 18.6 g of aniline and the mixture was heated for 30 min on a water bath. Then, with stirring and cooling a solution of 15.1 g of (I) in 30 ml of ether was added, the

Aryl (alkyl) Amides of Anthranilic Acid  and  a,b

(II) (IIa)

No.	Significance of R	M.p.[c]	Found, %			Calc., %			Yield %
			C	H	N	C	H	N	
1	C_6H_5	130° [7]: needles (from benzene)	—	—	—	—	—	—	94.3
2	o-$CH_3C_6H_4$	104—105 [10]; platelets	—	—	—	—	—	—	59.4
3	p-$CH_3C_6H_4$	149—150 [10]; needles	—	—	—	—	—	—	50.6
4	o-$CH_3OC_6H_4$	102—103; needles (from benzine)	69.27, 69.30	5.81, 5.70	11.55, 11.60	69.42	5.78	11.57	53.7
5	p-$CH_3OC_6H_4$	126—127; platelets	69.31, 69.46	5.50, 5.77	11.50, 11.69	69.42	5.78	11.57	99
6	α-$C_{10}H_7$	157—158; needles	77.92, 77.75	5.48, 5.59	10.80, 10.78	77.86	5.34	10.68	53.5
7	β-$C_{10}H_7$	196—197; needles	78.05, 77.66	5.62, 5.50	10.79, 10.59	77.86	5.34	10.68	57.7
8	$C_6H_5CH_2$ [d]	123—124; platelets	—	—	12.60, 12.49	—	—	12.39	61.9
9	2,4-$(CH_3)_2C_6H_3$	138 [10]; needles (from benzene)	—	—	—	—	—	—	76
10	2,4,6-$(CH_3)_3C_6H_2$	120—122; needles	—	—	11.07, 11.18	—	—	11.00	4.95
11	C_6H_5—CH—CH_3	105—106; platelets	75.21, 75.19	6.72, 6.71	11.67, 11.74	75.00	6.66	11.66	79.1
12	C_6H_5 [b]	155—156; platelets	—	—	9.69, 9.64	—	—	9.62	95
13	o-BrC_6H_4 [b]	191—192; platelets	—	—	7.73, 7.58	—	—	7.57	70
14	C_6H_5 [b]	211—212 [12]; long needles	—	—	—	—	—	—	88
15	R and R' = C_2H_5	73—74; platelets (from benzine)	68.70, 68.62	8.40, 8.44	14.25, 14.27	68.75	8.33	14.06	49.5
16	R = CH_3; R' = C_6H_5	127 [11] prisms (from benzene	—	—	—	—	—	—	66.6
17	R = C_6H_5; R' = $C_6H_5CH_2$	103—105; needles (from benzine)	79.64, 79.53	6.21, 6.15	9.24, 9.25	79.47	5.96	9.27	71

Notes: a) In Expts. 1-14 we obtained substance (II), in Nos. 15-17, substance (IIa); to obtain the latter we took the magnesyl amine RR'NMgX with R and R' as shown in the table; b) Expts. Nos. 1-11 and 15-17 were carried out with (I); in Expts. Nos. 12 and 13 the starting substance was methyl 5-bromoanthranilate; in Expt. No. 14, methyl 3,5-dibromoanthranilate. The formula for the product of Expts. Nos. 12 and 13 was  for Expt. No. 14,  ; c) substances for which a solvent is not shown were crystallized from alcohol; d) the alcohol solution of the product of Expt. No. 8 had a weak value fluorescence.

mixture was boiled for 30 min on a water bath, and decomposed with a saturated ammonium chloride solution. The ether layer was separated and the ether distilled off with steam; the residue crystallized from alcohol. Yield 20 g. Constants given in the table.

SUMMARY

1. We have studied the reaction between methyl anthranilate and magnesyl amines obtained from primary and secondary aliphatic, aromatic, and aliphatic-aromatic amines.

2. The availability of the starting substances and entirely satisfactory yields of reaction products permit us to recommend this reaction as a method of synthesis of aryl amides of anthranilic acid.

3. We have obtained a number of undescribed aryl amides of anthranilic acid and have studied their properties.

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SUBSTITUTED HYDRAZIDES OF HYDROXYCARBOXYLIC ACIDS

III. MONOACYL DERIVATIVES OF DIARYL AND DIALKYLGLYCOLIC ACID ARYLHYDRAZIDES

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2030-2032, June, 1960
Original article submitted June 4, 1959

In the aryl hydrazides of hydroxycarboxylic acids [1, 2] there are two hydrogens which can be substituted by acyl groups, the hydrogen on the nitrogen and on the hydroxyl group. For the characteristics of the chemical behavior of these groups of compounds we have studied the formation of acetyl and benzoyl derivatives with the acyl on the nitrogen. These compounds are of interest as substances with possible analgesic actions [3].

The acetyl derivatives were obtained by heating the corresponding arylhydrazides in acetic anhydride on a boiling water bath for 40-50 min. The optimum reaction time was found by acetylating the phenylhydrazide of benzilic acid with different periods of heating. The acetylation reaction proceeds rapidly and most of the acetyl derivative is already formed after 15-20 min. The N-acetyl derivatives of arylhydrazides of diaryl- and dialkylglycolic acids are shown in Table 1. These acetyl derivatives are colorless, crystalline substances, soluble in the usual organic solvents. Their melting points are higher than those of the corresponding starting arylhydrazides.

The benzoyl derivatives were obtained by heating the arylhydrazides with benzoyl chloride in benzene solution. The resulting benzoyl derivatives are shown in Table 2.

EXPERIMENTAL

β-Acetyl-β-phenylhydrazide of benzilic acid. (I). A solution of 1 g of phenylhydrazide of benzilic acid in 10 ml of acetic anhydride was heated for 40 min on a boiling water bath. After cooling, crystals precipitated. The substance was soluble in alcohol, glacial acetic acid, and toluene.

Substances (II-XII) were obtained in a similar way. It should be noted as characteristic that the β-acetyl-β-phenylhydrazide of dibenzylglycolic acid (V) did not dissolve in CCl_4 and dissolved with great difficulty in alcohol. Substances (VI), (VII), and (IX) dissolved very easily in alcohol and glacial acetic acid.

m-Toluic acid phenylhydrazide. To a solution of m-tolyl magnesium bromide prepared from 20.5 g of m-bromotoluene and 2.8 g of magnesium we added 5.0 g of the ethyl ester of oxalic acid β-phenylhydrazide. The reaction mixture was heated for 20 min on a water bath and decomposed with dilute hydrochloric acid. The reaction product was removed with ether. Yield 72.3%. Soluble in alcohol, toluene, glacial acetic acid, chloroform, and dioxane. Needles (from toluene) with m.p. 158-159°.

Found %: N 7.78, 8.17. $C_{22}H_{22}O_2N_2$. Calculated %: N 8.09.

β-Benzoyl-β-phenylhydrazide of benzilic acid (XIII). One g of the phenylhydrazide of benzilic acid was heated with 0.7 g of benzoyl chloride in benzene for 15 min. The reaction product was isolated in the form of a crystalline precipitate. Soluble in glacial acetic acid, difficultly soluble in alcohol, toluene, benzene. Substances (XIV)-(XVIII) were obtained in an analogous way.

TABLE 1

N-Acetyl Derivatives of Diaryl- and Dialkylglycolic Acid Arylhydrazides $C_6H_5N(COCH_3)-NH-CO-CR_2(OH)$

No.	R	M.p.	Solvent for recrystallization	Crystal form	Yield, %	Empirical formula	Results of analysis (calculated values in parentheses)
(I)	C_6H_5	226—227°	Glacial acetic acid	Needles	84.1	$C_{22}H_{20}O_3N_2$	C 72.95, 72.81 (73.33); H 5.54, 5.63 (5.56); N 7.64, 7.63 (7.78); act. H 1.9
(II)	p-$CH_3C_6H_4$	180—181	Alcohol	Platelets	88.1	$C_{24}H_{24}O_3N_2$	N 6.92, 7.01 (7.22); CH_3CO 11.28, 11.47 (11.08); act. H 2.09, 2.30
(III)	m-$CH_3C_6H_4$	175—176	Glacial acetic acid	Prisms	80.4	$C_{24}H_{24}O_3N_2$	CH_3CO 11.39 (11.08)
(IV)	o-$CH_3OC_6H_4$	148—151	Dilute acetic acid	Needles, clumped	89.7	$C_{24}H_{24}O_5N_2$	CH_3CO 10.55 (10.24)
(V)	$C_6H_5CH_2$	249—250	Glacial acetic acid	Platelets	89.3	$C_{24}H_{24}O_3N_2$	N 7.32, 7.41 (7.22); CH_3CO 11.24 (11.08)
(VI)	C_2H_5	132—133	Benzene	Needles	67.2	$C_{14}H_{20}O_3N_2$	N 10.73, 10.59 (10.61); CH_3CO 16.68 (16.28)
(VII)	C_3H_7	167—168	Toluene	Platelets	85.7	$C_{16}H_{24}O_3N_2$	N 9.74, 9.49 (9.59); CH_3CO 15.12 (14.73)
VIII)	iso-C_3H_7	189—190	Glacial acetic acid	Fine prisms	60.0	$C_{16}H_{24}O_3N_2$	CH_3CO 15.07, 15.25 (14.73)
(IX)	C_4H_9	173—174	Dilute alcohol	Clumps	86.9	$C_{18}H_{28}O_3N_2$	N 9.09 (8.75); CH_3CO 13.61 (13.44)
(X)	iso-C_5H_{11}	214—215	Glacial acetic acid	Needles	94.1	$C_{20}H_{32}O_3N_2$	N 8.35, 8.37 (8.05); CH_3CO 12.61 (12.36)
XI)	$C_{18}H_{17}$	143—144	Alcohol	Needles, clumped	76.4	$C_{26}H_{44}O_3N_2$	CH_3CO 9.73 (9.95)
(XII)	*	207—208	Acetic anhydride	Platelets	89.3	$C_{18}H_{27}O_3N_2$	N 6.82, 6.87 (7.02); CH_3CO 10.54 (10.78)

*Formula of substance XII p-$BrC_6H_4N(COCH_3)-NH-CO-C(C_4H_9)_2(OH)$.

TABLE 2

N-Benzoyl Derivatives of Diaryl- and Dialkylglycolic Acid Arylhydrazides

$$C_6H_5N(COC_6H_5)-NH-CO-CR_1(OH)$$

No.	R	M.p.	Crystal form	Yield, %	Empirical formula	% N	
						found	calc.
(XIII)	C_6H_5	246—247°	Needles	94.5	$C_{27}H_{22}O_3N_2$	7.26, 6.91	6.95
(XIV)	p-$CH_3C_6H_4$	223—225	Needles	92.3	$C_{29}H_{26}O_3N_2$	6.35	6.22
(XV)	$C_6H_5CH_2$	221—221.5	Needles	81.8	$C_{29}H_{26}O_3N_2$	6.32, 6.43	6.22
(XVI)	C_2H_5	207—208	Platelets	81.6	$C_{19}H_{22}O_3N_2$	8.75, 8.85	8.59
(XVII)	C_3H_7	220—222	Needles	85.7	$C_{21}H_{26}O_3N_2$	8.14, 7.98	7.91
(XVIII)	C_4H_9	242—243	Platelets	94.9	$C_{23}H_{30}O_3N_2$	7.56, 7.44	7.33

•Solvent for recrystallization, glacial acetic acid.

SUMMARY

We have synthesized a series of undescribed acetyl and benzoyl derivatives of arylhydrazides of dialkyl- and diarylglycolic acids and studied their properties.

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•Original Russian pagination. See C. B. translation.

THE DIRECTIVE ACTION OF SUBSTITUENTS IN THE FORMATION OF PHENYLPHENAZINE N-OXIDES. III

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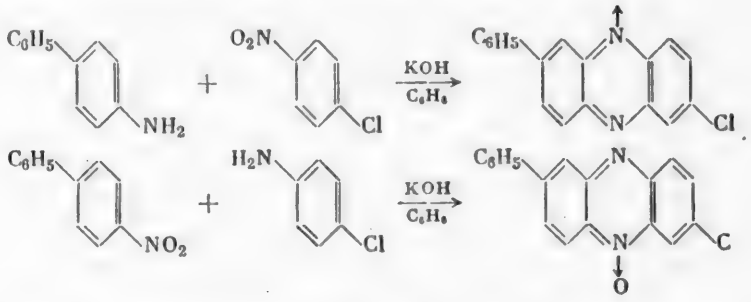
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2033-2040, June, 1960
Original article submitted June 3, 1959

In a previous communication [1] we reported the results of a study by a spectrophotometric method of the orienting effect of substituents (Cl and OCH_3) on the formation of phenazine N-monooxides. In the present paper are described results of an analogous study which was made on the N-monooxides of 1- and 2-phenylphenazines and their different substituents. For this purpose the method of alkaline condensation of the corresponding nitro and aminosubstituted benzenes, chlorobenzene, anisole, and diphenyl in benzene solution was used to prepare standard forms of 9- and 10-oxides of substituted phenylphenazines. Thus, for example, 9- and 10-oxides of 2-phenyl-6-chlorophenazine were prepared according to the following scheme:



The binary mixture of phenylphenazine N-monooxides needed for the investigation was obtained by oxidation of the base with 25% hydrogen peroxide in glacial acetic acid at 40-50°. From the mixture of oxidation products which usually consisted of unreacted base, N-monooxides and N,N-dioxide of the same base, the mixture of the two monooxides • was isolated by a chromatographic method. The quantitative ratio of isomeric monooxides in the mixture was determined by spectrophotometry according to Vierordt; the technique and method of determination were described in the previous communication [1].

In unsubstituted phenazine, nitrogen atoms 9 and 10 are equal in their ability to be oxidized by hydrogen peroxide. The introduction of the phenyl group in position 1 in the phenazine ring sharply destroys this equality. This is evident because in the oxidation of phenylphenazine (I) by hydrogen peroxide there is formed a mixture of isomeric N-monooxides with a very great predominance of one of them. By study of the absorption spectra of samples of the 9- and 10-oxides of 1-phenylphenazine, their natural and artificial mixtures (Fig. 1, 1-4), it was found (see table) that in the natural mixture the content of 9-oxide was only 7.3% and of the 10-oxide,

•In the remainder of the paper, this mixture of monooxides will be called the "natural mixture" in distinction from the "artificial mixture" prepared in the ratio of 1 : 1 as a control for each measurement.

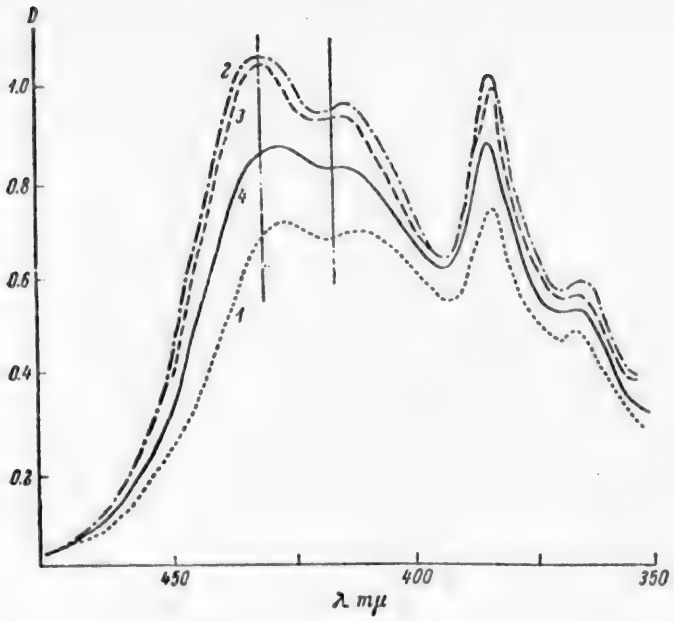


Fig. 1. Absorption spectra. 1) 1-Phenylphenazine 9-oxide; 2) 1-phenylphenazine 10-oxide; 3) natural mixture of 1-phenylphenazine N-monooxides; 4) artificial mixture of 1-phenylphenazine monooxides, 1 : 1 (alcohol, 10^{-4} M).

92.5%. The reason for such a sharp difference in ratio of formed monooxides of 1-phenylphenazines is not so much the electron influence of the substituent transmitted through the ring by the oxidation centers, the 9 and 10 nitrogen atoms, as the steric hindrance of the size of the substituent located along with the nitrogen atom 9. This last fact is just the decisive factor which determines the quantitative ratio of the isomers in the mixture of oxidation products.

Thus, the C_6H_5 group in position 1 of the phenazine ring orients the oxidation preferably on atom 10, which is free from the screening action of the substituent.

In 2-phenylphenazine (II) under analogous conditions, the oxidation ratio of the isomeric N-monooxides in the natural mixture is different: 39.7% of the 9-oxide and 60.1% of the 10-oxide. In this case, as is evident from these figures, the equality of the nitrogen atoms is also destroyed: the amount of 9-oxide is increased more than 5 times compared to the 1-phenylphenazine, and we obtained 1.5 times as much of the 10-oxide as of the isomeric 9-oxide of 2-phenylphenazine.

In the molecule of 2-phenylphenazine the spacial position of the substituent does not alter the formation of one or the other oxide; there remains only the electronic effect of the substituent, transmitted through the ring by the oxidation centers. In this case, judging by the greater yield of 10-oxide and the lesser of 9-oxide, the electrons which share in the formation of the N-oxide bond are drawn more by the substituent from the atom of nitrogen 9 and less from the atom of nitrogen 10. As a result of this, there is formed an unequal mixture of isomers in which the predominance of one isomer over the other can be considered a measure of the effect of the substituent on the molecule as a whole.

Thus, in 2-phenylphenazine in distinction from 1-phenylphenazine, the decisive factor in orienting the oxidation is the electronic nature of the substituent.

The oxidation of disubstituted phenazine derivatives into isomeric N-monooxides is an example of a complex orienting effect of two substituents and depends on the electron interaction of both substituents on the phenazine ring and for α-substituted derivatives, also on their steric distribution in the ring.

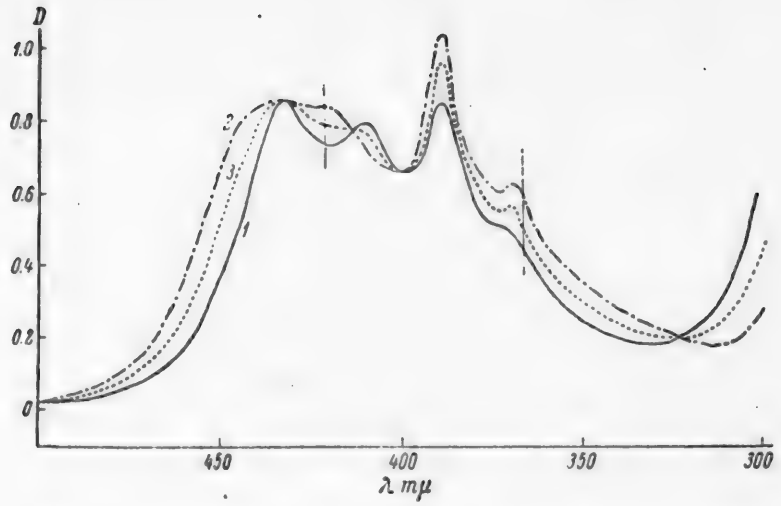
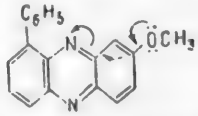


Fig. 2. Absorption spectra. 1) 1-Phenyl-7-chlorophenazine 9-oxide; 2) 1-phenyl-7-chlorophenazine 10-oxide; 3) artificial mixture of 1-phenyl-7-chlorophenazine N-monooxides 1 : 1 (alcohol 10^{-4} M).

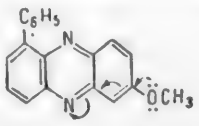
It was shown previously that the CH_3O group in position 7 (or 2) in the phenazine ring by its +C effect orients oxidation to the nitrogen atom 9, conjugated with it. The effect of the C_6H_5 group in position 1 shifts this for steric reasons and makes the oxidation of the molecule in this position difficult. The combined effect of the C_6H_5 and the CH_3O groups on the oxidation of disubstituted phenazines was studied in the example of oxidation of 1-phenyl-7-methoxyphenazine and other disubstituted compounds.

In the oxidation of 1-phenyl-7-methoxyphenazine (III) under conditions analogous to those described above, we found in the reaction products after chromatography, a greater amount of N-monooxides and a very small quantity of N,N-dioxide of 1-phenyl-7-methoxyphenazine. The natural mixture and the standard of 9- and 10-oxides of 1-phenyl-7-methoxyphenazine were studied by spectrophotometry in alcohol solution at the same concentrations. It was found that 1-phenyl-7-methoxyphenazine 9-oxide occurs in the mixture to the extent of 16.5% and the 10-oxide, 83.5%. It is clear from this that in the oxidation of 1-phenyl-7-methoxyphenazine, in spite of the spacial hindrance of the C_6H_5 group, almost twice as much of 9-oxide is formed as in 1-phenylphenazine (7.3%). This effect can be related only to the CH_3O group, which strengthens the ability of the nitrogen atom 9 to oxidation by supplying to it electrons through the conjugated chain:



Analogous results were obtained in the study of the mixtures of 9- and 10-oxides of 1-phenyl-7-chlorophenazine (V). From the curve of absorption spectra of the standard oxides and the binary mixture obtained by oxidation of the base in acetic acid by hydrogen peroxide, it was found that in the natural mixture there was 16.4% 9-oxide and 83.6% 10-oxide. It was found before [1] that on oxidation of 2-chlorophenazine the isomeric N-monooxides were formed almost equally in the mixture, with a slight predominance of the 9-oxide. In considering the case of 1-phenyl-7-chlorophenazine, the sharp decrease in yield of 9-oxide is connected with the screening action of the phenyl group in position 1 and the conjugation of the Cl atom with nitrogen atom 9, which in slight degree resists the action of the phenyl group.

We consider still another example of the orienting effect of two substituents, one of which is found in the α-position and the other in the β-position and conjugated with the nitrogen atom, free from steric hindrance.



This case occurs with 1-phenyl-6-methoxyphenazine, in which the CH_3O group by its +C effect supplies electrons to nitrogen atom 10, thus strengthening its ability to form the N-oxide bond, and the C_6H_5 group makes inaccessible to oxidation the second nitrogen atom, not conjugated with the methoxy group. A study of the absorption spectra of the natural and standard 9- and 10-oxides of 1-phenyl-6-methoxyphenazine showed that the curve of the mixture and the curve of 1-phenyl-6-methoxyphenazine 10-oxide fully agreed in wavelength and molar extinction, and a mixed sample melted without depression. This is possible only if there is no admixture of the second N-oxide. Hence, in the oxidation of 1-phenyl-6-methoxyphenazine the concordance of orientation by the substituents (steric action of C_6H_5 group and electron effect of the CH_3O group) leads to the formation only of 1-phenyl-6-methoxyphenazine 10-oxide.

We consider two more cases, when both substituents in the phenazine ring orient the oxidation only with the effect of the electron influence when the steric screening centers of oxidation of the molecule are excluded. In one case, in 2-phenyl-6-methoxyphenazine the observed effect can be explained from the point of view of reciprocal effect of the substituents on oxidation of the molecule; in the other case an explanation for the observed effect is not given.

In 2-phenyl-6-methoxyphenazine two substituents of a different electronic nature are acting. One of them (CH_3O), as was established above, by its +C effect favors oxidation in the nitrogen atom 10 conjugated with it. The other substituent (C_6H_5) by its −C effect weakens this ability on nitrogen atom 9. When their actions are combined, there is a relatively high electron density on nitrogen atom 10. In order to establish the ratio of 9- and 10-oxides of 2-phenyl-6-methoxyphenazine in the mixture of isomers, we studied the standard spectrum of the oxides separately and the spectrum of the isolated mixture in alcohol at the same concentration. The agreement of the results showed that the curve of monooxides isolated by chromatography and the curve of 2-phenyl-6-methoxyphenazine 10-oxide coincided fully, and therefore, calculations according to Vierordt were not needed; we obtained only the 10-oxide. The second isomer was practically not formed.

Oxidation of 2-phenyl-6-chlorophenazine (IV) is the second example of a complex orienting effect of two substituents which have a different electron influence on the oxidation centers and both are found in the β-position in the phenazine ring. One substituent (the Cl atom) by its −I effect draws electrons from both atoms of nitrogen, less from the nitrogen atom 10 conjugated with it. The second substituent (C_6H_5) by its −C effect weakens the ability of nitrogen atom 9 for oxidation. It was assumed that as a result of the combined effect of these substituents, the electron density on nitrogen atom 10 would be higher than on 9, and so on oxidation of 2-phenyl-6-chlorophenazine, there would be more 10-oxide and less 9-oxide in the mixture of N-monooxides. However, according to the experimental data, in the mixture of N-monooxides the ratio of isomeric oxides was the reverse of the expected, and we found 61.8% of the 9-oxide and 38.1% of the 10-oxide. We have not found a satisfactory explanation for this observation.

EXPERIMENTAL

The synthesis of 1-phenyl-, 1-phenyl-6-methoxy-, 1-phenyl-7-methoxy-, 1-phenyl-7-chloro-, 2-phenyl-, 2-phenyl-6-methoxyphenazine, the 9-oxide of 1-phenyl- and 2-phenylphenazine, and the 10-oxide of 1-phenyl- and 2-phenylphenazine was described in the work published earlier [2].

2-Phenyl-6-chlorophenazine. Two g of 2-phenyl-6-chlorophenazine 9-oxide was dissolved in 100 ml of toluene, and 75 ml of water, 7 ml of glacial acetic acid and 20 g of fresh iron filings were added. With energetic stirring and heating of the toluene to boiling, the reduction was complete in one hour. At the end of the reduction the intense yellow solution of toluene had almost decolorized (in a drop of sample on a milky glass appeared small crystals of bluish 2-phenyl-6 chlorophenazhydrin). Then the reduction reaction was stopped, the toluene layer was separated and the sludge was washed twice with hot toluene. The toluene extract was washed with water dried with calcium chloride, evaporated to a volume of 30 ml, and chromatographed on aluminum oxide. In the first zone from below (zone did not fluoresce under a quartz lamp) was located the 2-phenyl-6-chlorophenazine. In the second small zone with a clear fluorescence was found a small amount of unreacted 2-phenyl-6-chlorophenazine N-oxide. The base had the form of light yellow needles with m.p. 186°. The sulfate was red. In concentrated sulfuric acid it forms a green disalt, which on hydrolysis goes over to the red monosalt and then precipitates from solution in the form of the yellow base. Absorption maxima in alcohol occur at 235, 274, 378, 385, and 394 mμ.

Found %: N 9.83, 9.86. $C_{18}H_{11}N_2Cl$. Calculated %: N 9.64.

2-Phenyl-6-chlorophenazine 9-oxide was obtained by alkaline condensation from 51 g of p-aminodiphenyl, 63 g of p-nitrochlorobenzene, and 120 g KOH in 500 ml of benzene. We isolated from the second zone of the chromatogram 6.1 g (6.6%) of 2-phenyl-6-chlorophenazine 9-oxide with a clear yellow fluorescence. Yellow needles (from dioxane) with m.p. 204.5°; decomposes at 220°. In concentrated sulfuric acid it forms an easily hydrolyzed red salt. Absorption maxima occur at 242, 281, 380, 396, 418, and 442 mμ.

Found %: N 8.84, 8.88; Cl 11.69, 11.65. $C_{18}H_{11}ON_2Cl$. Calculated %: N 9.13; Cl 11.58.

2-Phenyl-6-chlorophenazine 10-oxide was obtained in an analogous way from 80 g of p-nitrodiphenyl, 38 g of p-chloroaniline, and 120 g KOH in 500 ml of benzene. From the third zone of the chromatogram we isolated 4.92 g (4%) of 2-phenyl-6-chlorophenazine 10-oxide with a yellow fluorescence. Yellow needles (from dioxane) with m.p. 224°; decomposes at 228°. Absorption maxima occur at 276, 292, 386, 399, and 432 mμ.

Found %: N 9.09, 9.17; Cl 11.81, 11.66. $C_{18}H_{11}ON_2Cl$. Calculated %: N 9.13; Cl 11.58.

1-Phenyl-7-chlorophenazine 9-oxide was obtained as above from 100 g of o-nitrodiphenyl, 51 g of p-chloroaniline, and 120 g KOH in 400 ml of benzene. From the third zone of the chromatogram we isolated 1.2 g (1%) of 1-phenyl-7-chlorophenazine 9-oxide. Yellow needles with m.p. 188° (decomposition). Absorption maxima at 210, 277, 370, 387, 409, and 430 mμ.

Found %: N 9.24, 9.28; Cl 11.49, 11.51. $C_{18}H_{11}ON_2Cl$. Calculated %: N 9.13; Cl 11.58.

1 Phenyl-7-chlorophenazine 10-oxide was obtained by alkaline condensation of 51 g of o-aminodiphenyl, 63 g of p-nitrochlorobenzene, and 120 g KOH in 500 ml of benzene. We isolated from the third zone of the chromatogram 8.5 g (9%) of 1-phenyl-7-chlorophenazine 10-oxide. Bright yellow needles with an intense yellow phosphorescence under a quartz lamp, m.p. 191°, decompose at 210°. They crystallize from a mixture of alcohol and dioxane (1 : 1). Absorption maxima at 222, 276, 368, 388, and 434 mμ.

Found %: N 9.31, 9.22; Cl 11.63, 11.72. $C_{18}H_{11}ON_2Cl$. Calculated %: N 9.13; Cl 11.58.

1-Phenyl-7-methoxyphenazine 9-oxide was obtained by alkaline condensation of 100 g of o-nitrodiphenyl, 50 g of p-anisidine, and 60 g of KOH in 500 ml of benzene. We isolated from the fourth zone of the chromatogram 1-phenyl-7-methoxyphenazine 9-oxide with a yield of 13.8 g (11.4%). Yellow needles with m.p. 199° (decomposition). They show a bright orange fluorescence under the quartz lamp. In concentrated sulfuric acid they form a red salt. Absorption maxima at 247, 277, 365, 382, 420, and 446 mμ.

Found %: N 9.23, 9.14. $C_{19}H_{14}O_2N_2$. Calculated %: N 9.27.

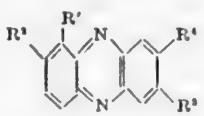
1-Phenyl-7-methoxyphenazine 10-oxide. We dissolved 0.3 g of 1-phenyl-7-methoxyphenazine in 50 ml of glacial acetic acid at 16-18° and added dropwise to the solution over the period of a half hour 10 ml of 25% hydrogen peroxide at the same temperature. At higher temperatures, a mixture of two monooxides is formed. At 16-18° 1-phenyl-7-methoxyphenazine 9-oxide is not formed. After addition of hydrogen peroxide the solution was stirred for 12 hr more and then diluted with 400 ml of water. After 24 hr the precipitate was filtered off, washed with water, and with a minimal amount of alcohol and ether. Yield 0.3 g. After chromatography from benzene on aluminum oxide we isolated from the first zone 0.13 g of unreacted base; from the second zone 0.17 g (54%) of 1-phenyl-7-methoxyphenazine 10-oxide. After two recrystallizations from alcohol the preparation had the form of small yellow needles with a strong yellow fluorescence, in distinction from the 9-oxide, which did not fluoresce at all; m.p. 201°, decomposition 206-207°. Absorption maxima at 224, 274, 370, 385, 429, and 446 mμ.

Found %: N 9.01, 8.99. $C_{19}H_{14}O_2N_2$. Calculated %: N 9.27.

2-Phenyl-6-methoxyphenazine 10-oxide and 1-phenyl-6-methoxyphenazine 10-oxide were described previously [2].

Oxidation of substituted phenazine derivatives and separation of the N-oxides. Phenyl-, methoxy-, and chlorophenazines were oxidized by the known method of I. Ya. Postovskii and E. I. Abramova [3] which they used for the preparation of the N-oxide of phenazine-1-carboxylic acid and its amide. To a solution of the substituted phenazine in glacial acetic acid with mechanical stirring at 40-50° for two hours was added dropwise

Directive Action of Substituents on the Oxidation of Mono- and Disubstituted Phenazines to the N-oxides



Substance No.	Substituents				Wave length at which mixtures were measured, mμ*	Found, %			
						in artificial 1 : 1 mixture		in natural mixture** (average values)	
	R¹	R²	R³	R⁴		9-oxide	10-oxide	9-oxide	10-oxide
I	C_6H_5	H	H	H	415and430	50.3	50.1	7.3	92.5
II	H	C_6H_5	H	H	410and430	48.7	51.3	39.7	60.1
III	C_6H_5	H	H	OCH_3	310and340	50.9	49.1	16.5	83.5
IV	H	C_6H_5	Cl	H	380and440	49.7	50.2	61.8	38.1
					330and345	50.6	49.3		
V	C_6H_5	H	H	Cl	367and420	48.6	51.4	16.4	83.6

*Shown by the vertical line in Figs. 1 and 2.

**Experimental data on content of 9-oxide and 10-oxide, respectively, %: (I) 7.3, 8.5, 6.1; 92.5, 91.6, 93.3. —(II) 40.5, 39.0, 38.4, 41.0; 59.5, 60.9, 61.8, 58.5. —(III) 16.2, 18.9, 15.7, 15.3; 84.2, 81.0, 84.3, 84.7. —(IV) 60.8, 61.4, 61.9, 64.8, 60.5, 61.9, 61.2; 39.1, 38.5, 38.1, 35.2, 39.4, 38.1, 38.8. —(V) 19.7, 12.3, 14.3, 17.5, 16.7, 17.1, 18.6, 15.2; 80.2, 87.7, 85.9, 82.5, 83.3, 82.9, 81.4, 84.8.

a 25% solution of hydrogen peroxide half diluted with glacial acetic acid. The reaction product was poured into water, the precipitate was filtered off, washed with water, and dried, then chromatographed from benzene on aluminum oxide. The zones were usually distributed in the following order: in the first zone, counting from the bottom up, was unoxidized base (zone without fluorescence); in the second zone was a yellow color, fluorescing strongly—a mixture of the two monooxides; and in the orange upper zone was the N,N-dioxide of the given base. The thus isolated N-monooxides were not crystallized, in order to avoid full or partial loss of one of the isomers, but were always analyzed for content of nitrogen or chlorine. After analysis, for preparation of the standard curves the N-monooxides were dissolved at a concentration of 10^{-4} M and subjected to photometry 3-5 times, until we obtained no less than three concordant results.

Example. To 0.64 g of 1-phenylphenazine in 32 ml of glacial acetic acid at 40-50° was added dropwise during two hours 5 ml of a 25% hydrogen peroxide solution, half diluted with acetic acid. The reaction mixture was poured into 400 ml of water and left overnight to crystallize. The precipitate was filtered, washed with water, and dried in a desiccator. The weight of the precipitate was 0.65 g. It was dissolved in 20 ml of benzene and put on a chromatographic column with aluminum oxide. From the first zone we isolated 0.37 g of 1-phenylphenazine, from the second 0.24 g of a mixture of the 9- and 10-oxides of 1-phenylphenazine. Small yellow needles with m.p. 180-183° decompose at 199-201°. From the third zone with an orange color we extracted 0.01 g of 1-phenylphenazine 9,10-dioxide.

Found %: N 10.25, 10.33. $C_{18}H_{12}ON_2$. Calculated %: N 10.29.

Spectrophotometric measurements of the natural mixture were carried out 3-8 times for each compound in concentrations equalling that of the standard N-monooxides. The standard curve was considered satisfactory for analysis only when the artificial mixture of known composition showed in calculation an error no greater than 2%. In the table we give the results of our measurements and calculations. The spectrophotometric measurements were carried out with a photoelectric spectrophotometer SF-4.

The author is grateful to A. I. Kirianov for his consideration in this work. I. B. Grebenyuk took part in the syntheses.

SUMMARY

Using a spectrophotometric method of analysis we have determined the orienting action of substituents in the molecules of mono- and disubstituted phenazines in their oxidation by hydrogen peroxide to N-monooxides. We have shown that the chief factor in orientation in an α-substituted phenazine is the steric factor, and the electron effect of the substituent plays a secondary role, especially for the nitrogen atom subjected to the screening action of the substituent. When two substituents act together, both in the β-position in the ring, the spacial effect does not play an important part, and the chief factor in orientation is the electron nature of the substituent.

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A STUDY OF THE POSSIBILITY OF REPLACING DIETHYL ETHER BY HIGHER BOILING SOLVENTS IN THE PREPARATION OF FERROCENE FROM CYCLOPENTADIENYL MAGNESIUM BROMIDE AND FERRIC CHLORIDE

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2040-2042, June, 1960
Original article submitted June 26, 1959

Dicyclopentadienyl iron, sometimes called ferrocene, is a new organometallic compound discovered in 1951 by Kealy and Pauson [1], with a high thermal stability and a content of up to 30% of organically bound iron. The use of ferrocene and its derivatives is very promising in the plastics and artificial fiber industries, since it can be expected that the introduction of ferrocene into a high polymer molecule will lead to an increase in its thermal stability and mechanical strength. As was noted by A. N. Nesmeyanov and É. G. Perevalova [2], the reaction of cyclopentadienylmagnesium bromide with metal halides is very suitable for obtaining cyclopentadienyl derivatives of metals, and, especially, of ferrocene. However, the existing difficulty with this method is the use in the synthesis of considerable amounts of low boiling solvent, diethyl ether, which almost excludes the possibility of using this method in industry.

The present study is devoted to an investigation of the possibility of replacing diethyl ether in preparing ferrocene from cyclopentadienyl magnesium bromide and ferric chloride by other, higher boiling solvents. At the same time we have worked out a new variant for obtaining ferrocene by condensation of cyclopentadienyl magnesium bromide with powdered $FeCl_2$. The work was carried out in two directions. 1) Synthesis of ferrocene using different solvents which boil higher than diethyl ether according to the scheme:

$$C_2H_5MgBr + C_5H_6 \longrightarrow C_5H_5MgBr + C_2H_6 \quad (1)$$

$$\left.\begin{aligned} 2C_5H_5MgBr + 2FeCl_3 &\longrightarrow 2FeCl_2 + C_5H_5{-}C_5H_5 + MgCl_2 + MgBr_2 \\ 2C_5H_5MgBr + FeCl_2 &\longrightarrow (C_5H_5)_2Fe + MgCl_2 + MgBr_2 \end{aligned}\right\} \quad (2)$$

2) Synthesis of ferrocene with preliminary reduction of $FeCl_3$ by chlorobenzene.

EXPERIMENTAL

The synthesis of ferrocene was carried out in an atmosphere of nitrogen dried and freed from contaminants. To the magnesium organic compound prepared from 6 g of Mg, 27 g of C_2H_5Br and 100 ml of solvent was added with stirring a solution of 16.5 g of cyclopentadiene (prepared by depolymerizing dicyclopentadiene) in the solvent (1 : 1 by volume). The reaction mixture was cooled to room temperature and then treated with a solution of 10 g of $FeCl_3$ in 100 ml of solvent. This process was also accompanied by spontaneous heating of the reacting substances. The reaction mixture was further stirred with heating on a water bath for one hour and on the next day was poured into a beaker with a saturated NH_4Cl solution and then transferred to a round bottom flask, capacity 3 liters, for distillation of the ferrocene with superheated steam. All the solvents used in this work were carefully dried.

TABLE 1

Solvent for first step	Solvent for $FeCl_3$	Yield of ferrocene, %
Diethyl ether	Diethyl ether	60.0
Di-n-butyl ether	Di-n-butyl ether	61.3
Diisoamyl ether	Diisoamyl ether	45.7
Anisole	Anisole	0
Phenetole	Phenetole	0
Anisole	Diethyl ether	48.0
Anisole	Dioxane	38.0
Phenetole	Dioxane	40.0
Triethylamine	Dioxane	33.4

TABLE 2

Solvent for first step	Conditions for carrying out second step	Yield of ferrocene, %
Diethyl ether	$FeCl_2$ without solvent	71.2
Tetrahydrofuran	The same	71.2
Anisole	" "	0
Anisole	$FeCl_2$ mixed with dioxane	36.6

Ferrocene was obtained only in the experiments with di-n-butyl and diisoamyl ethers in yields respectively of 61.3 and 45.7%. When we used anisole and phenetole, in spite of the complete solution of magnesium and isolation of almost theoretical amounts of ethane, we were unable to get ferrocene. However, with addition of dioxane to the reaction mixture in the second step of the synthesis even in the case of using anisole and phenetole, we obtained ferrocene with yields of 38 and 40%, respectively. We also used other mixed solvents which gave satisfactory yields of ferrocene. The results of this series of experiments are given in Table 1.

In the second series of experiments we added $FeCl_2$ obtained by reduction of $FeCl_3$ with chlorobenzene [3] to cyclopentadienyl magnesium bromide obtained in various solvents. The reduction of $FeCl_3$ was carried out as follows. A mixture of anhydrous $FeCl_3$ and chlorobenzene (in mole ratio 1 : 2) was heated in a flask with a reflux condenser in an atmosphere of dry nitrogen for two hours at an oil bath temperature of 130°. The reaction product was filtered on a Buchner funnel and washed with absolute diethyl ether in an atmosphere of dry nitrogen. The light gray crystalline powder of $FeCl_2$ was added to the previously prepared C_5H_5MgBr (see above) in equimolar ratio. The reaction mixture was heated with stirring on a water bath for 6-8 hr and then treated as described. It should be noted that in this case, if the C_5H_5MgBr was prepared in anisole, in order to carry out the condensation of the magnesium organic compound with $FeCl_2$ it is necessary to add another solvent (dioxane). The results of this series of experiments are given in Table 2.

SUMMARY

1. We have shown that in the preparation of ferrocene from cyclopentadienyl magnesium bromide and $FeCl_3$ diethyl ether can be replaced by some simple ethers (di-n-butyl ether, diisoamyl ether).

2. We have shown that when the slightly active cyclopentadienyl magnesium bromide is prepared in anisole or phenetole, the use of a different solvent (dioxane) in the second step makes possible its condensation with $FeCl_3$ with a satisfactory yield of ferrocene.

3. We have suggested a new variant of the synthesis of ferrocene from cyclopentadienyl magnesium bromide in various solvents with $FeCl_2$, which gives a higher yield of ferrocene than the method of Kealy and Pauson.

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AUTOCONDENSATION REACTIONS OF CYCLIC KETONES AND CONDENSATIONS WITH AMMONIA

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2042-2047, June, 1960
Original article submitted June 23, 1959

Cyclic ketones with 5, 6, 7, and more carbon atoms, which are similar in structure, differ strongly in reactivity, as can be seen, for example, by comparison of the equilibrium constants for the reactions of some cyclic ketones with hydrocyanic acid [1]. Among the cyclic ketones C_5-C_7, the cyclohexanones are the most reactive. In this connection it seems interesting to study the behavior of cyclopentanones and cycloheptanones in reactions of autocondensation and condensation with ammonia which we studied [2, 3] for cyclohexanone; in order to study the effect of substituents we also investigated autocondensations and condensations with ammonia for 2-, 3-, and 4-methylcyclohexanones.

In the autocondensation of cyclohexanone under the influence of solid sodium hydroxide under ordinary conditions there is formed a tricyclic product with the composition $C_{18}H_{30}O_3$ with one carbonyl and two hydroxyl groups, having the structure of 2-[2-(1-hydroxycyclohexyl)-1-hydroxycyclohexyl]-cyclohexanone. Successive splitting from the dihydroxyketone of two and one molecules of water give in good yields the corresponding tricyclic unsaturated ketones $C_{18}H_{26}O$, 2-[2-(Δ^1-cyclohexenyl)-cyclohexylidene]-cyclohexanone and dodecahydrotriphenylene [2].

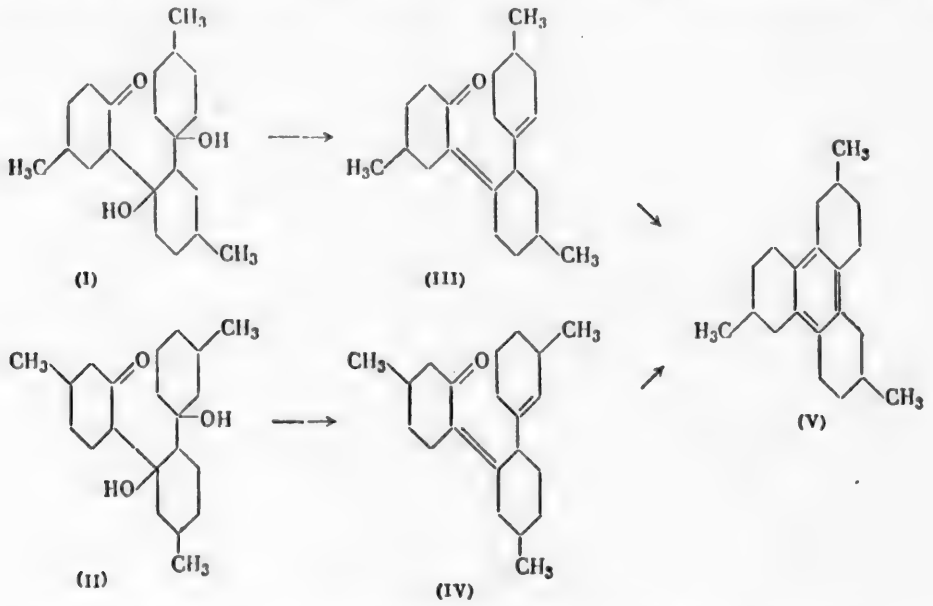
There is almost no indication of the formation of analogous products from other cyclic ketones. It is known only that when the vapors of 4-methylcyclohexanone are passed over a mixture of aluminum oxide and thorium oxide at 285° or when it is boiled with a methanol solution of sulfuric acid, there is formed 2,6,10-trimethyldodecahydrotriphenylene, whose properties, however, were not described. Autocondensation of 2- and 3-methylcyclohexanones under the same conditions did not give similar products [4].

In the reaction of cyclohexanone with ammonia at room temperature in the presence of ammonium chloride and calcium chloride, there was synthesized [3] 2,4-dipentamethylene-5,6-tetramethylene-2,3,4,5-tetrahydropyrimidine, from the hydrolysis product of which in an acid medium was isolated the β-aminoketone, 2-(1-aminocyclohexyl)-cyclohexanone. The latter in condensation with other carbonyl compounds and ammonia formed substituted tetrahydropyrimidines [5]. There is evidence that in the condensation of 3- and 4-methylcyclohexanones and also of cyclopentanone with ammonia at higher temperatures and pressures, there are obtained the corresponding diamines $C_{21}H_{36}N_2$ and $C_{15}H_{24}N_2$, without a discussion of their structures [6].

In the present work we show that in the autocondensation of cyclopentanone under the conditions described above, we obtain the previously known [7, 8] bicyclic ketone 2-cyclopentylidene-cyclopentanone, and the tricyclic ketone 2,5-dicyclopentylidene-cyclopentanone. Evidently in this case the dihydroxyketone which first forms is unstable and easily loses two molecules of water to go over into the unsaturated ketones.

4- and 3-Methylcyclohexanones in the presence of powdered sodium hydroxide form solid products: 2-[2-(1-hydroxy-4-methylcyclohexyl)-1-hydroxy-4-methylcyclohexyl]-4-methylcyclohexanone (I) and 2-[2-(1-hydroxy-5-methylcyclohexyl)-1-hydroxy-5-methylcyclohexyl]-5-methylcyclohexanone (II), respectively.

Under the influence of methanol-sulfuric acid, these dihydroxyketones split out two molecules of water and are converted into the unsaturated ketones (III) and (IV). When the latter are heated for one hour at 350°, they are converted into the same hydrocarbon, 2,6,10-trimethyldodecahydro-1,2,3,4,5,6,7,8,9,10,11,12-triphenylene (V).



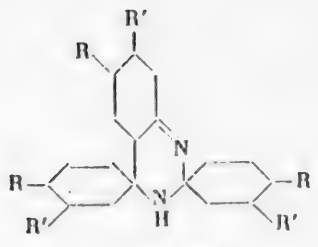
It is important to observe that 4-methylcyclohexanone differs little from cyclohexanone in rate of formation of the dihydroxyketone (I), while 3-methylcyclohexanone takes part in this reaction much more slowly. 2-Methylcyclohexanone in general does not form analogous products. The different behavior of the substituted cyclohexanones in the autocondensation reaction can be explained by steric factors. In 2-methylcyclohexanone the methyl group screens the carbonyl oxygen. In the case of 3-methylcyclohexanone the substituent prevents the attack of another ketone molecule on the hydrogen atom in position 2, and only those α-hydrogen atoms enter the condensation which occur in position 6. From this follows the decreased rate of autocondensation of 3-methylcyclohexanone compared to cyclohexanone. The fact that 4- and 3-methylcyclohexanones finally give the same 2,6,10-trimethyldodecahydrotriphenylene confirms the correctness of the assigned structural formulas. If in the reaction of formation of (II) the α-hydrogen atom in position 2 had reacted, we would have obtained from 3-methylcyclohexanone a dodecahydrotriphenylene in which the substituents would be arranged differently than in (V).

In the presence of solid sodium hydroxide at room temperature cycloheptanone does not undergo autocondensation.

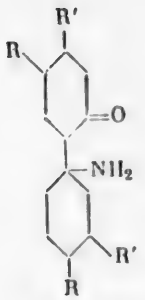
In the reaction with ammonia, the above cyclic ketones behave differently. Cyclopentanone under these conditions forms with ammonia a dark mixture with an unpleasant odor, not stable in air, from which individual substances could not be isolated.

In the condensation of 4- and 3-methylcyclohexanones with ammonia in the presence of ammonium and calcium chlorides, we obtained the undescribed, 2,4-di-(γ-methylpentamethylene)-5,6-(β-methyltetramethylene) (VI) and 2,4-di-(β-methylpentamethylene)-5,6-(γ-methyltetramethylene)-2,3,4,5-tetrahydropyrimidine (VII). From the products of acid hydrolysis of (VI) and (VII) we isolated the previously undescribed (VIII) and (IX). 2-Methylcyclohexanone does not form substituted tetrahydropyrimidine which, as in the case of the autocondensation, can be explained by steric factors.

From the reaction of cycloheptanone with ammonia there results apparently an unstable cycloheptylidene ketimine which is easily hydrolyzed by water into cycloheptanone and ammonia.



(VI, VII)



(VIII, IX)

(VI, VIII) R = CH_3, R′ = H
(VII, IX) R′ = CH_3, R = H

Thus, in the reactions of autocondensation and condensation with ammonia, cyclopentanone, cyclohexanone, its monomethyl substituted isomers, and cycloheptanone behave differently. The most reactive among these ketones are cyclohexanone and 4-methylcyclohexanone.

EXPERIMENTAL

Autocondensation of cyclopentanone. A mixture of 188 g of cyclopentanone and 20 g of solid sodium hydroxide stood for 40 days at room temperature. The resulting crystalline mass was filtered, washed with water, and air dried. We obtained 31 g (19%) of 2,5-dicyclopentylidene-cyclopentanone, m.p. 81-82° (from methyl alcohol) which agreed with the literature data [8]. The filtrate was diluted with water and extracted with ether. The ether solution was dried and the ether evaporated off with nitrogen; from the remaining red liquid (131 g) on standing in the cold we separated a further 15 g (9%) of the same ketone. Forty-seven g of the filtrate was vacuum distilled. We obtained 27 g (38%) of 2-cyclopentylidene-cyclopentanone, b.p. 118-120° (12 mm), $n^{20}D$ 1.5180 (according to the literature [8], b.p. 117-119° at 12 mm, $n^{20}D$ 1.5178) and 20 g of nondistilling, tarry residue.

2-[2-(1-Hydroxy-4-methylcyclohexyl)-1-hydroxy-4-methylcyclohexyl]-4-methylcyclohexanone (I). A mixture of 18 g of 4-methylcyclohexanone and 2 g of finely ground sodium hydroxide stood for four days with occasional shaking. After washing with water to a neutral reaction we diluted the white paste with 50 ml of methyl alcohol. The resulting precipitate was filtered, washed with 25 ml of methyl alcohol, and air dried. We obtained 6.5 g (36%) as a fine white powder with m.p. 160° (from benzene); insoluble in water, poorly soluble in methyl alcohol and ether, better in benzene.

Found %: C 75.23; H 10.38. Mol. wt. 340. $C_{21}H_{36}O_3$. Calculated %: C 74.95; H 10.78. Mol. wt. 336.5.

2-[2-(1-Hydroxy-5-methylcyclohexyl)-1-hydroxy-5-methylcyclohexyl]-5-methylcyclohexanone (II). From 18 g of 3-methylcyclohexanone and 2 g of solid sodium hydroxide after standing for 12 days and treatment as described above, we obtained a yield of about 8% as a white powder with m.p. 170° (from benzene) with properties analogous to those of substance (I).

Found %: C 75.35; H 10.58. Mol. wt. 345. $C_{21}H_{36}O_3$. Calculated %: C 74.95; H 10.78. Mol. wt. 336.5.

2-[2-(4-Methyl-Δ'-cyclohexenyl)-4-methylcyclohexylidene]-4-methylcyclohexanone (III). A mixture of 2 g of (I) and 1 ml of concentrated sulfuric acid in 10 ml of methyl alcohol stood for one hour. The resulting paste was washed with water to a neutral reaction and then with 10 ml of methyl alcohol. After vacuum drying we obtained 1.4 g (78%) as a semisolid white product; insoluble in water, poorly soluble in methyl alcohol, better in ether.

Found %: C 84.17; H 10.74. Mol. wt. 312. $C_{21}H_{32}O$. Calculated %: C 83.73; H 10.73. Mol. wt. 300.5.

2-[2-(5-Methyl Δ'-cyclohexenyl)-5-methylcyclohexylidene]-5-methylcyclohexanone (IV). In an analogous manner from a mixture of 1 g of (II) and 0.5 ml of concentrated sulfuric acid we obtained (IV) with a yield of about 67%, in the form of a white, semisolid mass with properties like those of (III).

Found %: C 84.23; H 10.85. Mol. wt. 310. $C_{21}H_{32}O$. Calculated %: C 83.73; H 10.73. Mol. wt. 300.5.

2,6,10-Trimethyldodecahydro-1,2,3,4,5,6,7,8,9,10,11,12-triphenylene (V). One g of substance (III) was heated for one hour at 350°. After washing with a small amount of ether we obtained 0.6 g (64%) with m.p. 195°

(from benzene). From 1 g of substance (IV) under the same conditions we obtained substance (V) with a yield of 53% and m.p. 195° (from benzene). A mixed sample gave no m.p. depression.

2,4-Di-(γ-methylpentamethylene)-5,6-(β-methyltetramethylene)-2,3,4,5-tetrahydropyrimidine (VI). Into a mixture of 23 g of 4-methylcyclohexanone, 25 ml of methyl alcohol, 2 g of calcium chloride, and 1 g of ammonium chloride, ammonia was passed for 24 hr at 0° with stirring. The mixture was poured into water and extracted with ether. The ether solution was dried, most of the ether was evaporated off with nitrogen, and the residue was removed in a vacuum. We obtained 19 g (87%) of a very viscous yellowish mass, insoluble in water, soluble in many organic solvents; easily hydrolyzed by acids even in the cold.

Found %: C 80.10; H 11.42. Mol. wt. 310. Equiv. 160. $C_{21}H_{36}N_2$. Calculated %: C 79.68; H 11.46. Mol. wt. 316.5. Equiv. 158.2.

2,4-Di-(β-methylpentamethylene)-5,6-(γ-methyltetramethylene)-2,3,4,5-tetrahydropyrimidine (VII). From 3-methylcyclohexanone under the same conditions we obtained (VII) with a yield of 55% with properties analogous to those of (VI).

Found %: C 79.95; H 11.47. Mol. wt. 309. Equiv. 161. $C_{21}H_{36}N_2$. Calculated %: C 79.68; H 11.46. Mol. wt. 316.5. Equiv. 158.2.

2-(4'-Methyl-1'-aminocyclohexyl)-4-methylcyclohexanone (VIII). Ten g of substance (VI) was dissolved in 120 ml 0.5 N hydrochloric acid. After 24 hr the solution was treated with ether (5 times with 25 ml). Ammonia was passed into the water layer to an alkaline reaction, and the oil which separated was extracted with ether. The ether solution was dried, most of the ether was evaporated off with nitrogen and the rest in a vacuum. We obtained 5 g (76%) of a viscous yellowish liquid, poorly soluble in water, easily in the usual organic solvents.

d^{20}_4 0.988, $n^{20}D$ 1.4950, MR_D 66.00; calc. 65.88.

Found %: C 75.63; H 11.38. Equiv. 224. $C_{14}H_{25}ON$. Calculated %: C 75.27; H 11.28. Equiv. 223.4.

2-(4'-Methyl-1'-acetylaminocyclohexyl)-4-methylcyclohexanone [from acetic anhydride and (VIII)], m.p. 140° (from aqueous methyl alcohol).

2-(3'-Methyl-1'-aminocyclohexyl)-5-methylcyclohexanone (IX). From 10 g of substance (VII) and 115 ml of 0.5 N hydrochloric acid in an analogous way we obtained (IX) with a yield of 68% and with properties like those of (VIII).

d^{20}_4 0.982, $n^{20}D$ 1.4930; MR_D 66.08; calc. 65.88.

Found %: C 75.73; H 11.47. Equiv. 225. $C_{14}H_{25}ON$. Calculated %: C 75.27; H 11.28. Equiv. 223.4.

2-(3'-Methyl-1'-acetylaminocyclohexyl)-5-methylcyclohexanone, m.p. 144° (from aqueous methyl alcohol).

SUMMARY

1. In the autocondensation of 4- and 3-methylcyclohexanones under the influence of solid sodium hydroxide with the usual conditions we synthesized the tricyclic products: the dihydroxyketones 2-[2-(1-hydroxy-4-methylcyclohexyl)-1-hydroxy 4-methylcyclohexyl]-4-methylcyclohexanone and 2-[-2-(1-hydroxy-5-methylcyclohexyl)-1-hydroxy-5-methylcyclohexyl]-5-methylcyclohexanone. Splitting two molecules of water from these diketones gave the α,β-δ,ε-unsaturated ketones 2-[2-(4-methyl-Δ'-cyclohexenyl)-4-methylcyclohexylidene]-4-methylcyclohexanone and 2-[2-(5-methyl-Δ' cyclohexenyl)-5-methylcyclohexylidene]-5-methylcyclohexanone. At high temperature these form the same hydrocarbon, 2,6,10-trimethyldodecahydro-1,2,3,4,5,6,7,8,9,10,11,12-triphenylene.

2. The condensation of 4-and 3-methylcyclohexanones with ammonia in the presence of calcium and ammonium chlorides gives the substituted 2,3,4,5-tetrahydropyrimidines: 2,4-di-(γ-methylpentamethylene)-5,6-(β-methyltetramethylene)-2,3,4,5-tetrahydropyrimidine and 2,4-di-(β-methylpentamethylene)-5,6-(γ-methyltetramethylene)-2,3,4,5-tetrahydropyrimidine. From the products of hydrolysis of these we isolated the β-aminoketones 2-(4'-methyl-1'-aminocyclohexyl)-4-methylcyclohexanone and 2-(3'-methyl-1'-aminocyclohexyl)-5-methylcyclohexanone.

3. 2-Methylcyclohexanone and cycloheptanone do not form dihydroxyketones under the conditions of autocondensation of the other ketones and substituted 2,3,4,5-tetrahydropyrimidines are not formed by their treatment with ammonia.

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HALOARYLATIONS OF UNSATURATED COMPOUNDS WITH AROMATIC DIAZO COMPOUNDS

XI. POLAROGRAPHY AND ABSORPTION SPECTRA OF SOLUTIONS OF PHENYL AND p-TOLYLDIAZONIUM CHLORIDES WITH CUPRIC CHLORIDE

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2047-2051, June, 1960
Original article submitted June 4, 1959

It is known that in reactions of haloarylation of unsaturated compounds by aromatic diazo compounds, the conditions needed usually require the presence of cupric chloride.

In the absence of the latter the reaction scarcely occurs, for it takes another direction. The chlorides of other metals ($SnCl_2$, $CoCl_2$, $NiCl_2$, $FeCl_3$, $MnCl_2$, $HgCl_2$, $CdCl_2$, $ZnCl_2$) also show no action [1, 2].

There is no clear explanation of how $CuCl_2$ permits the reaction of chloroarylation. Meerwein [3], who discovered this reaction, considered haloarylation as an ionic process, but did not explain the role of $CuCl_2$. In the opinion of Koelsch [4], $CuCl_2$ takes part in some sort of oxidation-reduction reaction which precedes the addition of halogen and aryl radicals at the double bond. Kochi [5] in general considers that not $CuCl_2$ but Cu_2Cl_2 formed by reduction with acetone has a catalytic action on the reaction. It is difficult to agree with this explanation since the aryldiazonium chlorides themselves are oxidizers; also the reaction occurs successfully in the absence of acetone [6].

A. V. Dombrovskii and A. P. Terent'ev [7], considering the ability of aryl diazonium chlorides to form complexes with the chlorides of a number of metals [8], suggested as an explanation of the reaction mechanism that in the chloroarylation of unsaturated compounds there is first formed a complex of this type between the diazonium salt and the cupric chloride. This is the more likely if we consider that cupric chloride, which has paramagnetic properties, tends to form complex compounds.

At the present time, no complexes between aryl diazonium chlorides and $CuCl_2$ have been isolated. In this connection it seems interesting to establish a chemical reaction between these compounds.

The polarographic study and determination of absorption spectra of mixtures of solutions of cupric chloride and diazonium salts carried out in the present work confirm, in our view, the suggestion of such a reaction and the resulting role of cupric chloride in the haloarylation reaction.

For the study we prepared the dry salts phenyl diazonium chloride (I) and p-tolyl diazonium chloride (II) by the method described by Hirsch [9].

Polarographic measurement was carried out on a polarograph of the type PV-1. The sensitivity of the galvanometer was $2.5 \cdot 10^{-9}$ a/mm/m. The characteristics of the capillary were 2.335 $mg^{2/3}$ $sec^{-1/2}$. As a base we used 1.0 N sodium chloride solution. Before polarography nitrogen was passed through the solution to be studied, for 20 min. The potential was determined relative to a saturated calomel electrode. Measurements were made at 0°.

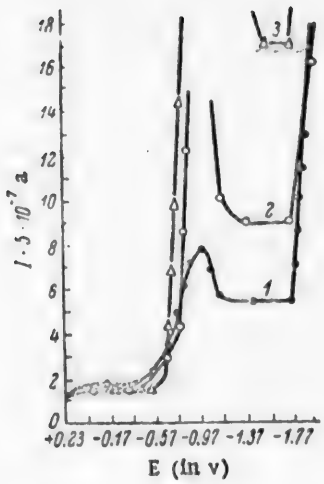

Fig. 1. Polarogram of solutions of $C_6H_5N_2Cl$ (I). 1) 10 ml 1.0 N NaCl + 0.5 ml 0.1 N (I); 2) the same + 0.5 ml (I); 3) the same + + 1 ml (I).

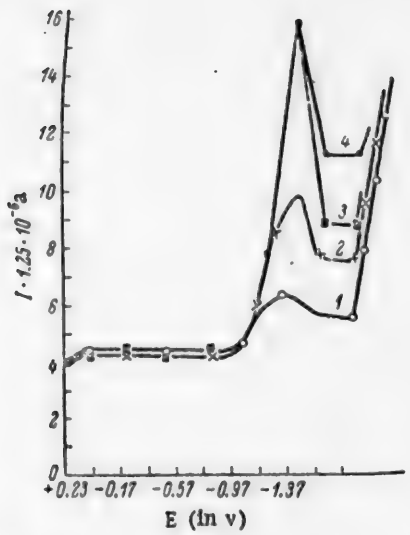

Fig. 2. Polarogram of solutions of $p\text{-}CH_3C_6H_4N_2Cl$ (II). 1) 10 ml 1.0 N NaCl + 0.5 ml 0.1 N (II); 2) the same + 0.5 ml (II); 3) the same + 0.5 ml (II), the same + + 1 ml (II).

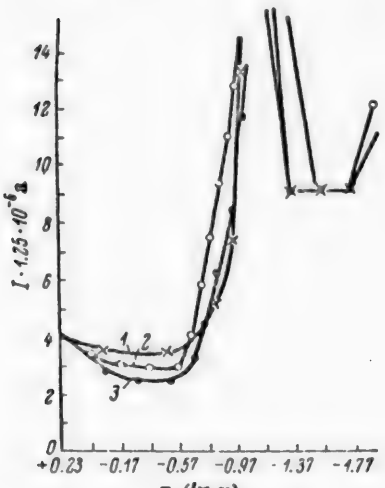

Fig. 3. Polarogram of a mixture of solutions of $C_6H_5N_2Cl$ (I) and $CuCl_2$. 1) 10 ml of 0.1 N NaCl + 3 ml (I) + 1 ml $CuCl_2$; 2) the same + 1 ml $CuCl_2$; 3) the same + 1 ml $CuCl_2$.

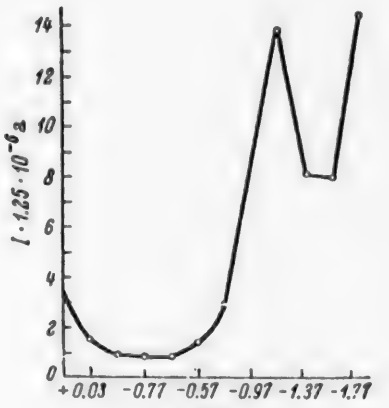

Fig. 4. Polarogram of a mixture of solutions of $p\text{-}CH_3C_6H_4N_2Cl$ (II) and $CuCl_2$ (10 ml 1.0 N NaCl + 2 ml (II) + + 2 ml $CuCl_2$).

We obtained polarograms for solutions of cupric chloride, phenyl diazonium chloride, p-tolyl diazonium chloride and mixtures of these diazonium salts with cupric chloride. The half wave potential of reduction of copper was + 0.03 v which agreed well with the literature data [10].

Phenyl diazonium chloride was reduced on a dropping mercury electrode, giving a polarogram with a maximum (Fig. 1) which was not suppressed by gelatine. At first, reduction corresponded to a potential of −0.57 v, then followed a sharp rise in current strength, and after the maximum there was clearly shown an area of diffusion current.

p-Tolyl diazonium chloride was reduced at a more negative potential, which evidently is due to the presence of the methyl group (Fig. 2). At first reduction occurred at a potential of −0.97 v. The presence of a maximum in this case also makes it difficult to determine the half wave potential. Both for (I) and for (II) the value of the limiting current depends in linear fashion on concentration of diazonium salt in the interval studied.

In polarography of a mixture of solutions of $CuCl_2$ + (I) and $CuCl_2$ + (II) we obtained curves shown in Figs. 3 and 4, respectively. The nature of the curves for both mixtures was the same. With increasing potential at first occurred a lessening of current strength. With further increase in potential the curves agreed in character with the corresponding curves for pure diazonium salts. The order of the shifting did not affect the course of the curves.

Thus, in the polarogram of the mixture of solutions of $CuCl_2$ + (I) and $CuCl_2$ + (II) the wave characteristic for Cu^{++} ions is absent. Evidently the copper ion is bound in a complex which is not reduced at the given potential. The fact that at potentials corresponding to the limiting current for the copper wave there is a fall in current strength can be thus explained: that the complex ion in whose composition the copper is found is negatively charged. This anion near the point of zero charge of the mercury is repelled from the electrode, so that the current strength is decreased. An analogous fall in current strength near the point of zero charge was found by other authors [11] in polarography of anions of persulfate and other anions. This fall was also explained from the point of view of overcharging the surface of the cathode.

Such an explanation of the polarogram of mixtures of solutions of $CuCl_2$ and ArN_2Cl (Ar = C_6H_5 or p-$CH_3C_6H_4$) confirms the suggestion that cupric chloride forms a complex with aryl diazoniums. The reaction evidently can be expressed by the following scheme:

$$2ArN_2Cl + CuCl_2 \longrightarrow [ArN_2]_2CuCl_4 \rightleftarrows 2[ArN_2]^+ + CuCl_4^{--}.$$

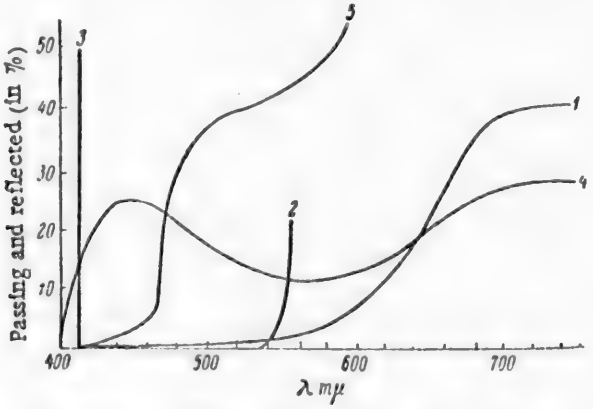

Fig. 5. Absorption spectra curves. 1) $CuCl_2$; 2) $C_6H_5N_2Cl$ (I); 3) p-$CH_3C_6H_4N_2Cl$ (II); 4) $CuCl_2$ + (I); 5) $CuCl_2$ + (II).

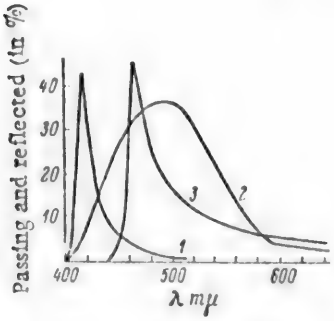

Fig. 6. Absorption spectra curves. 1) $FeCl_3$; 2) p-$O_2NC_6H_4N_2Cl$; 3) p-$O_2NC_6H_4N_2Cl \cdot FeCl_3$.

The formation of a complex compound is also indicated by the change in absorption spectrum of a mixture of $CuCl_2$ + ArN_2Cl compared to the spectra for the separate components. The measurements were carried out on a self recording spectrophotometer at 0-5°C.*

In Fig. 5 we give the absorption spectra for $CuCl_2$, (I), and (II) and also for mixtures of solutions of $CuCl_2$ + (I) and $CuCl_2$ + (II). For solutions of $CuCl_2$ the absorption maximum lies in the region of 680 mμ (curve 1). Practically colorless solutions of (I) and (II) in the visible region do not absorb (curves 2 and 3). The maximum in the curves of the mixtures of aryl diazonium chloride with $CuCl_2$ is markedly shifted in the short wave part of the spectrum compared to the maximum for $CuCl_2$ (curves 4 and 5). The shift

*N. O. Pastushak took part in the experimental work.

in the maximum for the absorption curves is evidently related to the fact that the Cu^{++} ion, which determines the color, forms a complex uncolored ion (probably $CuCl_4^{--}$) in the presence of ArN_2Cl and this leads to the hypsochromic shift in the maximum of the absorption curve.

In this connection it is interesting to compare the absorption spectra curves which we obtained for solutions of $FeCl_3$, $p\text{-}O_2NC_6H_4N_2Cl$, and the well known complex $p\text{-}O_2NC_6H_4N_2Cl \cdot FeCl_3$ [12] (Fig. 6). Here also there is a shift in the maximum of the absorption curve of the complex salt (curve 3) compared to the absorption maximum for $FeCl_3$ (curve 1). However, the shift is toward the long wave side (bathochromic shift) which is explained by the influence of the NO_2 group, a strong chromophore.

SUMMARY

1. Phenyl diazonium chloride and p-tolyl diazonium chloride are reduced on the dropping mercury electrode.

2. Polarographic study and study of the absorption spectra of mixtures of solutions of phenyl diazonium chloride and p-tolyl diazonium chloride with cupric chloride, and also of the separate components shows that these diazonium salts form complex compounds with cupric chloride.

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HORMONES OF THE THYROID GLAND AND THEIR ANALOGS

V. A NEW SYNTHESIS OF β-THYROXINE

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2051-2055, June, 1960
Original article submitted March 9, 1959

It is well known that the thyroxine molecule can undergo considerable structural change in the side chain while retaining hormonal activity [1, 2]. In this respect it is of definite interest to study the physiological activity of β-thyroxine, since, due to the excellent work of V. M. Rodionov, β-amino acids have become much more available as synthetic compounds than the corresponding α-isomers.

β-Thyroxine was first prepared in 1952 by Cookson and Green [3] by a rather complex scheme, including in the next to the last stage the Posner reaction, which takes place with very poor yields. The substance did not have antithyroid activity and the hormonal activity of the preparation was not studied.

Since this method does not permit accumulation of enough of the substance for biological study, we decided to carry out a synthesis of β-thyroxine from the easily available β-tyrosine, the preparative method for which was worked out previously by us [4]. β-Tyrosine (I) was nitrated to the 3,5-dinitro derivative (II) which by successive acetylation and esterification was converted to the ethyl ester of N-acetyl-3,5-dinitro-β-tyrosine (III). For formation of the β-thyronine group we used the elegant method of preparing dinitrodiphenyl ethers worked out by Borrows and co-workers [5]. For this purpose the p-toluene sulfonate of ethyl N-acetyl-3,5-dinitro-β-tyrosinate (IV) was converted into the quaternary pyridinium salt (V) and the latter was condensed with the monomethyl ether of hydroquinone. The resulting substituted dinitro-β-thyronine (VI) was hydrogenated, and both amino groups were replaced through the diazo compound by two atoms of iodine. As a result of boiling the thus prepared compound (VII) with a mixture of hydrobromic acid and acetic acid there occurred saponification of the ester and amide bonds and formation of 3,5-diiodo-β-thyronine (VIII). Iodination of the latter with iodine in ethylamine solution led to obtaining β-thyroxine (IX). All the steps in this synthesis occur with sufficiently good yields.

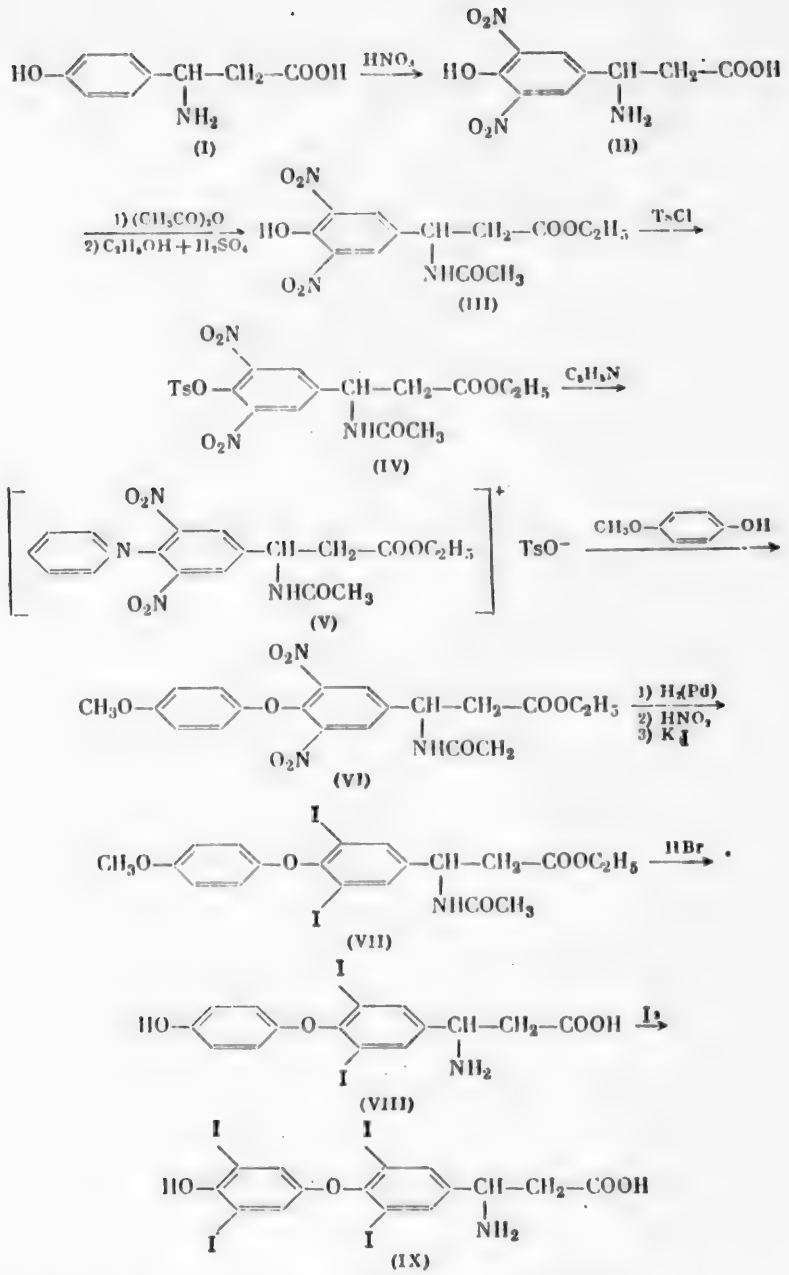
Biological study of β-thyroxine as its sodium salt carried out in the All-Union Research Institute for Experimental Endocrinology under the direction of S. M. Leites • showed that the sodium salt of β-thyroxine in doses of 2-4 mg/kg did not change the gas metabolism in rats in 24 hr after injection of the preparation.

Comparison of α- and β-thyroxine showed that in this case we have found loss of hormonal activity in going from the α-amino acid to the β-amino acid. It is curious to note that the antithyroid (antithyrotropic) activity of α- and β-diiodotyrosine is similar.

EXPERIMENTAL

3,5-Dinitro-β-tyrosine (II). We added 29.1 g of β-tyrosine (I) gradually with stirring to 120 ml of concentrated sulfuric acid at 10°. The reaction mass was then cooled to −5° and 23.7 ml of nitric acid (d 1.4) was

• We use this opportunity to thank S. M. Leites and his co-workers for carrying out these investigations.



added dropwise during one hour; the mixture was stirred for 15 min and poured onto ice. The mixture was carefully neutralized with 5 N sodium hydroxide and the crystals which precipitated were filtered off. The precipitate was washed with water to the disappearance of reaction for the sulfate ion. The yield of technical 3,5-dinitro-β-tyrosine was 26.35 g. After reprecipitation through the hydrochloride we obtained 24.5 g (56.2%). The substance did not have a characteristic melting point.

Found %: C 39.85; H 3.32; N 15.23. $C_9H_9O_7N_3$. Calculated %: C 39.85; H 3.32; N 15.40.

N-Acetyl-3,5-dinitro-β-tyrosine. We dissolved 25.4 g of 3,5-dinitro-β-tyrosine (II) in 405 ml of 1 N sodium hydroxide and at 15° added dropwise 17.8 ml of acetic anhydride. The solution was then stirred at room temperature for three hours until the odor of acetic anhydride disappeared. At the end of the reaction the product was separated by the action of 79 ml of 18% hydrochloric acid. The precipitate was filtered, washed with water to a neutral reaction to Congo, and recrystallized from aqueous alcohol. Yield 21.8 g (74.4%). M.p. 198.5-199.5°.

Found %: C 42.42, 42.05; H 3.31, 3.45; N 13.20; 13.55. $C_{11}H_{11}O_8N_3$. Calculated %: C 42.14; H 3.51; N 13.41.

Ethyl ester of N-acetyl-3,5-dinitro-β-tyrosine (III). We boiled 111.6 g of N-acetyl-3,5-dinitro-β-tyrosine under reflux with 1674 ml of anhydrous alcohol and 1.5 ml of concentrated sulfuric acid for three hours. The mixture was then cooled and poured into five times the volume of ice water and neutralized with a solution of sodium hydroxide. The precipitate was filtered and washed with water. After recrystallization from water, the yield was 64.7 g (53.3%). M. p. 138-139°.

Found %: C 45.60; H 4.35; N 12.62. $C_{13}H_{15}O_8N_3$. Calculated %: C 45.74; H 4.39; N 12.31.

Tosylate of the ethyl ester of N-acetyl-3,5-dinitro-β-tyrosine (IV). A mixture of 64.7 g of ester (III), 36.2 g of p-toluene sulfonyl chloride, 21.6 g of sifted, freshly ignited potash, and 647 ml of anhydrous acetone was boiled under reflux for one hour. At the end of the reaction the potash was filtered off and the acetone distilled off in a vacuum. The tarry residue was stirred with ether. The yield of technical product was 88.8 g. After recrystallization from anhydrous alcohol we obtained 72.7 g (76.6%). M. p. 136-137°.

Found %: S 6.26. $C_{20}H_{21}O_{10}N_3S$. Calculated %: S 6.38.

Quaternary pyridinium salt (V). Five g of the tosylate (IV) and 1.07 ml of anhydrous pyridine were refluxed for three hours at 98-100°. At the end of the reaction the solid, glassy mass was ground with ether. Yield 5.4 g (93.2%).

Ethyl ester of N-acetyl-β-[4-(4'methoxyphenoxy)-3,5-dinitrophenyl]-β-alanine (VI). A mixture of 40.4 g of the quaternary salt (V), 25.45 g of monomethyl ether of hydroquinone, 19.5 g of sifted, freshly ignited potash, and 450 ml of anhydrous acetone was refluxed for two hours. At the end of the reaction the potash was filtered off, the acetone was evaporated in vacuum, and the residue was dissolved in chloroform. The chloroform solution was washed with 2 N sodium hydroxide, then with water, and dried with calcium chloride. The solvent was distilled off in a vacuum. The residue was ground with ether and recrystallized from aqueous acetone (1 : 1). Yield 23 g (43.6%). M.p. 128-128.5°.

Found %: C 53.96; H 4.74; N 9.31. $C_{20}H_{21}O_9N_3$. Calculated %: C 53.69; H 4.69, N 9.39.

Ethyl ester of N-acetyl-β-[4-(4'-methoxyphenoxy)-3,5-diiodophenyl]-β-alanine (VII). We hydrogenated 20.5 g of the dinitro compound (VI) in 820 ml of methyl alcohol over palladium black at 70 atm and room temperature to complete stoppage of absorption of hydrogen. After hydrogenation was complete, the catalyst was filtered off, the methyl alcohol was evaporated in a vacuum in a current of carbon dioxide gas. The tar which formed was converted to a powder by stirring. Yield 17.6 g.

This diamino derivative was dissolved in 50 ml of acetic acid and the resulting solution was added dropwise at 10-20° to 17.6 ml of concentrated H_2SO_4.

At the same time we prepared a solution of 7.63 g of sodium nitrite in a mixture of 51.5 ml of concentrated H_2SO_4 and 115 ml of glacial acetic acid and to it at 0-2° we added dropwise during one hour the above solution of diamino compound; we stirred it at this temperature for one more hour. The resulting mass was quickly added to an emulsion of 50 ml of chloroform in a mixture of 11.1 g of iodine, 13.3 g of sodium iodide, 16.6 of urea in 216 ml of water, and the mixture was stirred for one hour at 20°. The reaction product was further extracted with chloroform, the chloroform extract was washed with a solution of sodium sulfite and water and dried with calcium chloride. After this, the chloroform was evaporated in a vacuum, the residue was ground with ether, and crystallized from alcohol. Yield 11.85 g (42.8%). M. p. 108-109°.

Found %: I 41.86, 41.95. $C_{20}H_{21}O_5NI_2$. Calculated %: I 41.71.

3,5-Diiodo-β-thyronine (VIII). Two g of ethyl ester (VII) was boiled with a mixture of 10 ml of distilled 47% hydrobromic acid and 10 ml of glacial acetic acid for ten hours. At the end of the reaction the acid was evaporated off in a vacuum to small volume. The precipitating hydrobromide was filtered, dissolved in 52.5 ml of aqueous hydrochloric acid (1 : 9) with heat, and the 3,5-diiodo-β-thyronine was precipitated with a saturated solution of sodium acetate. The precipitate was filtered, washed with water, alcohol, and ether. Yield 1.6 g (92%). The substance foamed at 225°, then solidified, and again melted at 290-291°.

Found %: I 47.68, 47.61. $C_{15}H_{13}O_4NI_2$. Calculated %: I 48.38.

β-Thyroxine (IX). We dissolved 0.47 g of 3,5-diiodo-β-thyronine (VIII) in 5 ml of 33% water solution of ethylamine with mild heating (about 30-35°) and added dropwise a solution of iodine (0.5 g) in 3 ml of a saturated solution of potassium iodide. After it was kept for a half hour at room temperature, β-thyroxine was precipitated by adding 6 ml of 50% acetic acid to pH 6. The yield of technical β-thyroxine 0.67 g. M.p. 178° (decomp.). β-Thyroxine was purified by its solution in a mixture of 1 part of 2 N NaOH and 2.5 parts of alcohol with heating, and acidification with 50% acetic acid to pH 6. Yield 0.4 g (57.5%). M. p. 211° (decomp., capillary immersed at 200°).

Found %: I 64.84, 64.61. $C_{15}H_{11}O_4NI_4$. Calculated %: I 65.38.

SUMMARY

We have carried out a new synthesis of β-thyroxine.

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INDOLE DERIVATIVES

VII. MECHANISM OF THE E. FISCHER REACTION

STRUCTURE OF THE ISOMERIC Bz-ETHYL-1,2,3-TRIMETHYLINDOLES

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2055-2061, June, 1960
Original article submitted June 9, 1959

We previously showed that when the asymmetrical methylphenylhydrazone of methylethyl ketone was heated with acetic anhydride in the presence of p-toluenesulfonic acid, there was formed along with methylacetanilide and β-acetyl-α-methyl-α-phenylhydrazine a mixture of isomeric Bz-acetyl-1,2,3-trimethylindoles [1]. On the basis of data of infrared spectroscopy, it was suggested that the isomer with m.p. 113.5-114.5° was 6- or 4-acetyl-1,2,3-trimethylindole, the isomer with m.p. 101.5.-102.5° was 7-acetyl-1,2,3-trimethylindole, and, finally, the substance which melted at 125-126.5° was 5-acetyl-1,2,3-trimethylindole. However, in the same work it was shown that these conclusions were not final and required experimental verification.

For this purpose all three isomers were reduced according to Kishner to the corresponding Bz-ethyl-1,2,3-trimethylindoles. For identification of the resulting substances we carried out a supplementary synthesis of three (of the four theoretically possible) Bz-ethyl-1,2,3-trimethylindoles. By direct comparison of the infrared spectra and also as a result of the mixed melting points of the indoles and their picrates we showed that the substance obtained by reduction of the isomer with m.p. 101.5-102.5° was 5-ethyl-1,2,3-trimethylindole. The synthetic 7-ethyl-1,2,3-trimethylindole was different from the products of Kishner reduction of the other two isomers, which thus should be the 4- and 6-isomers. In order to choose between them structurally, we carried out the synthesis of 6-ethyl-1,2,3-trimethylindole, which was identical with the indole obtained by Kishner reduction of the isomer with m.p. 125-126.5°. Thus the remaining acetylindole isomer with m.p. 113.5-114.5° should be 4-acetyl-1,2,3-trimethylindole.

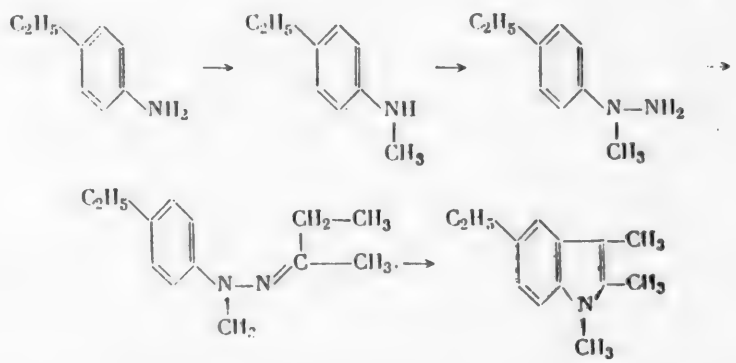
These results show that in distinction to the analogous regularities in the aminoacetophenone series [2], the strongest shift of the carbonyl band toward lower frequency is found for 6-acetyl-1,2,3-trimethylindole (1656 cm^{-1}, that is, meta-substitution with respect to the nitrogen), then comes 5-acetyl-1,2,3-trimethylindole (1662 cm^{-1}, p-substitution with respect to the nitrogen), and the least shift occurs for 4-acetyl-1,2,3-trimethylindole (1680 cm^{-1}). These results confirm the opinion of A. P. Terent'ev and M. N. Preobrazhenskaya [3] who suggested that the transmission of the effect of the nitrogen atom in the indole molecule to the benzene ring occurs in two ways: at the C–N bond with normal orientation in the para- and ortho-positions with respect to nitrogen, and by the system of bonds C–CH = CH–N with meta-orientation to the latter, and in the second case the effect of the nitrogen atom is considered stronger in position 6 than in position 5 of the indole molecule.

Our results also force a review of the question of orientation by substituents in the reaction of C-acetylation in the indole series. In the work of Plant and co-workers [4] it was shown that acetylation of indole in the tetrahydrocarbazoles under the conditions of the Friedel-Crafts reaction leads to 6-acetyl substitution in the benzene ring. An analogous conclusion was reached by N. F. Kucherov, V. P. Evdakov, and N. K. Kochetkov [5] in a study

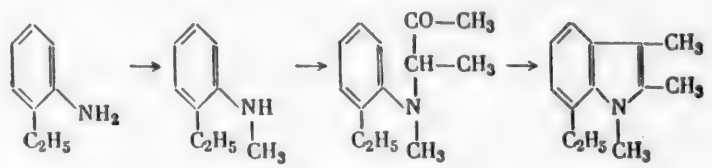
of the formylation of tetrahydrocarbazoles. On the other hand Borsche and Groth [6] declared that in the acetylation of indole homologs by the Friedel-Crafts method the 5-acetyl derivatives were first formed. Thus, when acetyl chloride acted on 1,2,3-trimethylindole in the presence of anhydrous aluminum chloride, these investigators obtained a substance with m.p. 123° (dinitrophenylhydrazone m.p. 258°) to which without any proof they assigned the structure of 5-acetyl-1,2,3-trimethylindole. As we showed above, this substance, which has the constants of our high-melting isomer, is not 5-, but 6-acetyl-1,2,3-trimethylindole. Thus, the conclusion of Borsche and Groth as to the preferential acetylation of indole in position 5 is incorrect. Our study using chromatography showed that acetylation of 1,2,3-trimethylindole in the presence of an acid catalyst (p-toluenesulfonic acid) leads to a mixture of 6-, 5-, and 4-substituted isomers with predominance of the 6-isomer, which agrees completely with the above mentioned ideas of A. P. Terent'ev and M. N. Preobrazhenskaya. Unfortunately, we did not succeed in isolating 7-acetyl-1,2,3-trimethylindole. It is possible that its formation cannot take place or it is formed in very small amounts because of spacial difficulties.

In conclusion, we give the scheme for carrying out our syntheses of the isomers of Bz-ethyl-1,2,3-trimethylindoles.

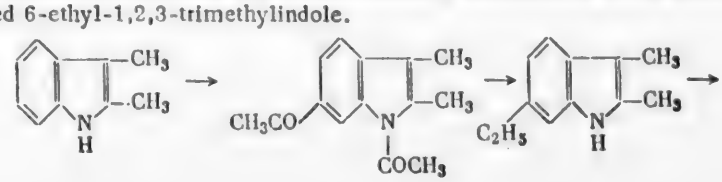
5-Ethyl-1,2,3-trimethylindole was obtained by the reaction of E. Fischer according to the scheme

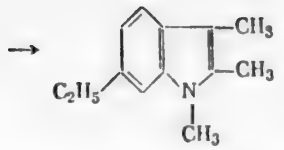


The attempt to obtain 7-ethyl-1,2,3-trimethylindole by this scheme was not successful, since reduction by zinc dust in acetic acid of 2-(N-nitrosomethylamino)-ethylbenzene gave instead of the expected hydrazine, the starting 2-methylaminoethylbenzene. Therefore the latter was condensed with methyl-α-bromoethyl ketone and the product of the condensation was converted by the Janetzky-Verkade reaction [7] into the required 7-ethyl-1,2,3-trimethylindole.



The most difficult synthesis was that of 6-ethyl-1,2,3-trimethylindole, since the reaction of E. Fischer and Bischler could not be used due to simultaneous formation of the 4-isomer. This problem was solved as follows. 6-Ethyl-2,3-dimethylindole was obtained by a series of steps from 1,4-diethylbenzene [4]. However, the yield in the last step (Madelung reaction) was so small that methylation of the resulting substance was impossible. Then 2,3-dimethylindole was submitted to acetylation by acetic anhydride in the presence of p-toluenesulfonic acid. A substance was isolated from the reaction mixture which from its melting point was 1,6-diacetyl-2,3-dimethylindole. After Kishner reduction we obtained ethyl-2,3-dimethylindole, identified as the 6-ethyl-2,3-dimethylindole previously obtained from 1,4-diethylbenzene. Methylation of this substance in liquid ammonia gave the required 6-ethyl-1,2,3-trimethylindole.





We express our thanks to Yu. N. Sheinker for carrying out the spectroscopic study.

EXPERIMENTAL

All the isomeric ethylanilines used in this work were obtained from pure crystalline nitroacetophenones by the Kishner reaction.

4-(p-Toluenesulfamido)-ethylbenzene. To a solution of 10 g of p-ethylaniline in 300 ml of pyridine was gradually added 18 g of p-toluenesulfonyl chloride. The reaction mixture became very hot. When it had cooled, it was poured with stirring and cooling into 750 ml of 10% hydrochloric acid. The red oil which precipitated gradually crystallized; the crystals were filtered and washed with water to a neutral reaction. Weight 21 g. Yield 91%. M.p. 90.5-91.5° (from aqueous alcohol).

Found %: C 65.10, 64.95; H 6.17, 6.00; N 5.15, 5.27. $C_{15}H_{17}O_2NS$. Calculated %: C 65.45; H 6.17; N 5.09.

N-Methyl-4-(p-toluenesulfamido)-ethylbenzene. We methylated 21 g of 4-(p-toluenesulfamido)-ethylbenzene in 115 ml of 1 N sodium hydroxide with 14 g of dimethylsulfate. The oil which precipitated gradually crystallized. The substance was filtered off, washed with 40 ml of 1 N sodium hydroxide, and then with water to a neutral reaction. Yield 18.5 g (83.5%). M.p. 66.5-67.5° (from alcohol).

Found %: C 66.56, 66.29; H 6.07, 6.20; N 5.07, 5.08. $C_{16}H_{19}O_2NS$. Calculated %: C 66.43; H 6.55; N 4.84.

4-Methylaminoethylbenzene. Four g of N-methyl-4-(p-toluenesulfamido)-ethylbenzene was boiled with a mixture of 25 ml of concentrated sulfuric acid, 5 ml of 95% acetic acid, and 28 ml of water for five hours. Then the reaction mass was cooled and poured into 250 ml of cold water. The water solution was made alkaline to pH 9 with a solution of sodium hydroxide, the amine was steam distilled and extracted with ether (about 300 ml). The ether solution was dried with ignited sodium sulfate, the ether was distilled off, and the residue was distilled in a vacuum. Pale yellow oil. B.p. 83-84° at 4 mm, d^{20} 0.9535, $n^{20}D$ 1.5490. Weight 1.6 g (48%).

Found %: C 79.87, 79.78; H 9.42, 9.30; N 10.67, 11.00. $C_9H_{13}N$. Calculated %: C 80.00; H 9.62; N 10.37.

N-Nitroso-4-methylaminoethylbenzene. To a solution of 4 g of 4-methylaminoethylbenzene in 3.7 ml of concentrated HCl with energetic stirring and a temperature which did not exceed −5° we added dropwise a solution of 2.06 g of sodium nitrite in 8.5 ml of water. When the amount of sodium nitrite had been added, the reaction mass was stirred one hour at room temperature and then the nitroso compound was extracted with 150 ml of benzene. The benzene was distilled off and the remaining yellow oil distilled in a vacuum. B.p. 97-97.5° at 1 mm. Weight 4 g (83.5%).

Found %: C 66.00; H 7.42; N 17.38. $C_9H_{12}ON_2$. Calculated %: C 65.85; H 7.32; N 17.07.

Asym -N-Methyl-(4-ethylphenyl)-hydrazine. To a suspension of 6.4 g of zinc dust in 9 ml of water we added gradually with energetic stirring and a temperature not above 10°, in the course of one hour, a solution of 4 g of N-nitroso-4-methylaminoethylbenzene in 9 ml of acetic acid. Then it was stirred for 45 min at room temperature and the reaction mass was heated to 80°. The unreacted zinc dust was filtered off and washed three times with 30 ml of 5% hydrochloric acid. The mother liquor was made alkaline with a 25% ammonia solution and the asym -N-methyl-(4-ethylphenyl)-hydrazine was extracted with 400 ml of ether. After distillation of the ether the remaining light yellow oil was vacuum distilled. B.p. 112-114° at 2 mm. Weight 2.55 g. Yield 70%.

The asym-N-methyl-(4-ethylphenyl)-hydrazine hydrochloride had m.p. 145-146°.

Found %: Cl' 18.63. $C_9H_{14}N_2 \cdot HCl$. Calculated %: Cl' 19.03.

5-Ethyl-1,2,3-trimethylindole. We boiled 2.3 g of asym -N-methyl-(4-ethylphenyl)-hydrazine with 6 ml of methylethyl ketone for one hour. The excess methylethyl ketone was distilled off. The remaining oil (2.8 g) was boiled for four hours with a solution of 2.6 ml of concentrated sulfuric acid in 15 ml of anhydrous alcohol. The reaction mass was poured into 150 ml of cold water, and the product was extracted with 200 ml of ether. The ether solution was dried with ignited magnesium sulfate, the solvent was distilled off, the residue was vacuum distilled. B.p. 122-123° at 1 mm. Weight 1.05 g (40%).

Found %: C 83.39; H 9.11; N 8.21. $C_{13}H_{17}N$. Calculated %: C 83.42; H 9.09; N 7.48.

The infrared spectrum of the synthesized 5-ethyl-1,2,3-trimethylindole agreed with the infrared spectrum of the ethyl-1,2,3-trimethylindole obtained by reducing the isomer of Bz-acetyl-1,2,3-trimethylindole with m.p. 101.5-102.5° by the Kishner method.

We obtained the picrate of 5-ethyl-1,2,3-trimethylindole in the form of dark red crystals with m.p. 118.5-119° (from alcohol).

Mixed samples of the picrate of 5-ethyl-1,2,3-trimethylindole with the picrate from the Kishner-reduced low melting Bz-acetyl-1,2,3-trimethylindole (m.p. 101.5-102.5°) showed no depression of melting point. Mixed melting point samples from the picrate of 5-ethyl-1,2,3-trimethylindole and the picrates of the other indoles obtained by Kishner reduction of the remaining Bz-acetyl-1,2,3-trimethylindoles (m.p. 113.5-114.5° and 125-126.5°) showed depression of the melting point.

2-(p-Toluenesulfamido-ethylbenzene. Obtained by analogy with 4-(p-toluenesulfamido)ethylbenzene. M.p. 133-134° (from aqueous alcohol). Yield 72%.

Found %: C 65.28, 65.14; H 6.40, 6.39; N 4.99. $C_{15}H_{17}O_2NS$. Calculated %: C 65.45; H 6.17; N 5.09.

N-Methyl-2-(p-toluenesulfamido)-ethylbenzene. 2-(p-Toluenesulfamido)-ethylbenzene was methylated with dimethylsulfate as in the case of N-methyl-4-(p-toluenesulfamido)-ethylbenzene. M.p. 76-76.5° (from alcohol). Yield 76%.

Found %: C 66.54, 66.94; H 6.47, 6.62; N 4.74. $C_{16}H_{19}O_2NS$. Calculated %: C 66.43; H 6.55; N 4.84.

2-Methylaminoethylbenzene. Obtained analogously to 4-methylaminoethylbenzene. Yield 61%. B.p. 54-56° at 1 mm.

Found %: C 79.70, 80.00; H 9.59, 9.74; N 10.61. $C_9H_{13}N$. Calculated %: C 80.00; H 9.62; N 10.37.

N-Nitroso-2-methylaminoethylbenzene. Obtained in the same way as the para-isomer. Yield 75%. B.p. 104-106° at 4 mm.

Found %: C 65.89, 65.98; H 7.40, 7.21; N 17.69, 17.80. $C_9H_{12}ON_2$. Calculated %: C 65.85; H 7.32; N 17.07.

The resulting nitroso compound was reduced by the method carried out for asym -N-methyl-(4-ethylphenyl)-hydrazine. The oil which remained after distillation of the ether was vacuum distilled. B.p. 66-69° at 2.5 mm. Weight 9 g. The p-toluenesulfonyl derivative obtained from this substance had m.p. 72.5-73.5° and gave no melting point depression with N-methyl-2-(p-toluenesulfamido)-ethylbenzene.

2-[(o-Ethylphenyl)-methylamino]-3-butanone. To a mixture of 6 g of 2-methylaminoethylbenzene and 5.6 g of sodium bicarbonate in 32 ml of alcohol at 80° was added during three hours 6.84 g of methyl- α-bromoethyl ketone (b.p. 40-45° at 2.5 mm). The reaction mass was heated at this temperature for another 4 hr, the alcohol was distilled off, and the residue was cooled to 5°. At this temperature, the reaction mass was acidified with 60 ml of 20% hydrochloric acid and the mixture was extracted with ether. The hydrochloric acid solution was kept cool and made alkaline with 20% sodium hydroxide to a pH of 9; the product was then extracted with ether (about 400 ml). The ether solution was dried with ignited sodium sulfate, the ether was distilled off, and the remaining red oil was vacuum distilled. B.p. 70-71° at 2.5 mm. Weight 6.5 g. Yield 71.5%.

Found %: C 76.30, 76.64; H 9.30, 9.60. $C_{13}H_{19}ON$. Calculated %: C 76.09; H 9.26.

The infrared spectrum contained a carbonyl band at 1712 cm^{-1}.

7-Ethyl-1,2,3-trimethylindole. A mixture of 6.5 g of 2-[(o-ethylphenyl)-methylamino]-3-butanone with 0.163 g of anhydrous zinc chloride was heated in a stream of nitrogen at 195-200° for two hours. Then the reaction mass was cooled and acidified with 60 ml of 4 N hydrochloric acid. The red oil which precipitated was extracted with ether. The extract (about 300 ml) was washed with 4 N hydrochloric acid and water to a neutral reaction, dried with magnesium sulfate, and the ether was distilled off. The remaining oil was vacuum distilled. B.p. 110-115° at 3 mm. M.p. 42.5-43.5° (from alcohol). Weight 2.1 g. Yield 35.5%.

Found %: C 83.40, 83.04; H 9.27, 9.23; N 7.39, 7.54. $C_{13}H_{17}N$. Calculated %: C 83.42; H 9.09; N 7.43.

The infrared spectrum of 7-ethyl-1,2,3-trimethylindole differed from the infrared spectra of all the isomers obtained by the Kishner reaction from Bz-acetyl-1,2,3-trimethylindoles.

The picrate consisted of dark red crystals with m.p. 118-119.5° (from alcohol).

Found %: C 54.15, 54.25; H 4.78, 4.92; N 14.53. $C_{13}H_{17}N \cdot C_6H_2OH(NO_2)_3$. Calculated %: C 54.81; H 4.80; N 13.47.

The picrate of 7-ethyl-1,2,3-trimethylindole gave a melting point depression when mixed with the picrates of any of the other isomers.

1,6-Diacetyl-2,3-dimethylindole. Ten g of 2,3-dimethylindole, 0.28 g of p-toluenesulfonic acid monohydrate and 70 ml (70.4 g) of acetic anhydride were boiled for one hour. To the still hot solution was added 0.15 g of crystalline sodium acetate, the acetic anhydride was distilled off in a vacuum and the residue was treated with 100 ml of water. The substance was extracted with four portions of ether of 100 ml each. After the ether solution had been dried with magnesium sulfate, the ether was distilled off and the residue was vacuum distilled. The first fraction had b.p. 145-155° at 2 mm (2 g), a colorless, crystalline substance. The second fraction with b.p. 155-190° at 2 mm (3.6 g) was a thick yellow oil which after stirring with absolute ether gave a crystalline substance. Weight 1.5 g. M.p. 114.5-116° (after three recrystallizations from alcohol). The literature value [4]: 1,6-diacetyl-2,3-dimethylindole, m.p. 116°.

Found %: C 72.63; H 6.19; N 6.09, 6.19. $C_{14}H_{15}O_2N$. Calculated %: C 73.35; H 6.11; N 6.55.

The mother liquors were combined and chromatographed on aluminum oxide. We isolated four substances whose structures are still unknown.

6-Ethyl-2,3-dimethylindole. A mixture of 4 g of 1,6-diacetyl-2,3-dimethylindole, 2.44 g of sodium hydroxide, 2.44 g of hydrazine hydrate, and 80 ml of diethylene glycol was boiled for one hour. Then heating was continued with simultaneous distillation of water until the temperature of the reaction mixture reached 190-200°. At this temperature it was boiled for three hours. After cooling, we added 120 ml of water and distilled the reduction product with steam. The distillate was extracted with ether. After drying with sodium sulfate and distillation of the ether, we obtained a crystalline substance. Weight 3 g (86%). M.p. 72.5-73.5° (from aqueous alcohol).

Found %: N 7.89. $C_{12}H_{15}N$. Calculated %: N 8.09.

A sample of the mixed melting point from 6-ethyl-2,3-trimethylindole and a commercial sample synthesized from p-diethylbenzene [4] gave no depression. The infrared spectra agreed completely.

6-Ethyl-1,2,3-trimethylindole. In 10 ml of liquid ammonia was dissolved 0.26 g of metallic sodium. To the resulting blue solution we added in small portions with stirring a suspension of 2 g of 6-ethyl-2,3-dimethylindole in 40 ml of absolute ether. At the end of the addition of the indole, the ammonia solution became colorless. We stirred for 20 min more and added a solution of 2.48 g of methyl iodide in 5 ml of absolute ether; stirring continued for three hours. To the reaction mixture we added 50 ml of ether, the ether solution was washed with water to a neutral reaction, and dried with magnesium sulfate. The ether was distilled off and the residue vacuum distilled. B.p. 110-113° at 5 mm. Weight 1.4 g (62.5%).

Found %: C 83.22, 83.86; H 9.17, 8.78; N 7.82, 7.91. $C_{13}H_{17}N$. Calculated %: C 83.42; H 9.09; N 7.43.

The infrared spectrum agreed with the infrared spectrum of the indole obtained from Kishner reduction of the isomeric Bz-acetyl-1,2,3-trimethylindole with m.p. 125-126.5°.

The picrate of 6-ethyl-1,2,3-trimethylindole consisted of dark red needles with m.p. 119.5-120° (from alcohol). A mixed m.p. with the picrate of the Kishner- reduced high melting isomer gave no depression, and with the picrates of the other Bz-acetyl-1,2,3-trimethylindoles, it gave a depression.

SUMMARY

1. We have synthesized isomeric Bz-ethyl-1,2,3-trimethylindoles and with them have shown the structures of the Bz-acetyl-1,2,3-trimethylindoles, the products of the reaction of the asymmetric methylphenyl hydrazone of methylethyl ketone with acetic anhydride.

2. We have shown that acetylation of 2,3-substituted indoles in the presence of acid catalysts leads to a mixture of isomers with predominance of the 6-acetyl substituent.

3. We have shown that the substance described by Borsche and Groth as 5-acetyl-1,2,3-trimethylindole is actually the 6-isomer.

4. We have established that in the infrared spectra of the isomeric Bz-acetyl-1,2,3-trimethylindoles, the strongest shift of the carbonyl band toward a lower frequency occurs for the 6-acetyl substituent, which indicates a transmission of the effect of the tertiary nitrogen in the base through the conjugated system of pyrrole bonds to the benzene ring.

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STEROIDS

VII. MECHANISM OF THE CONVERSION OF SOLASODINE TO THE ACETATE OF $\Delta^{5,16}$-PREGNADIENOL-3β-ONE-20*

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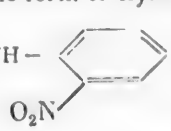
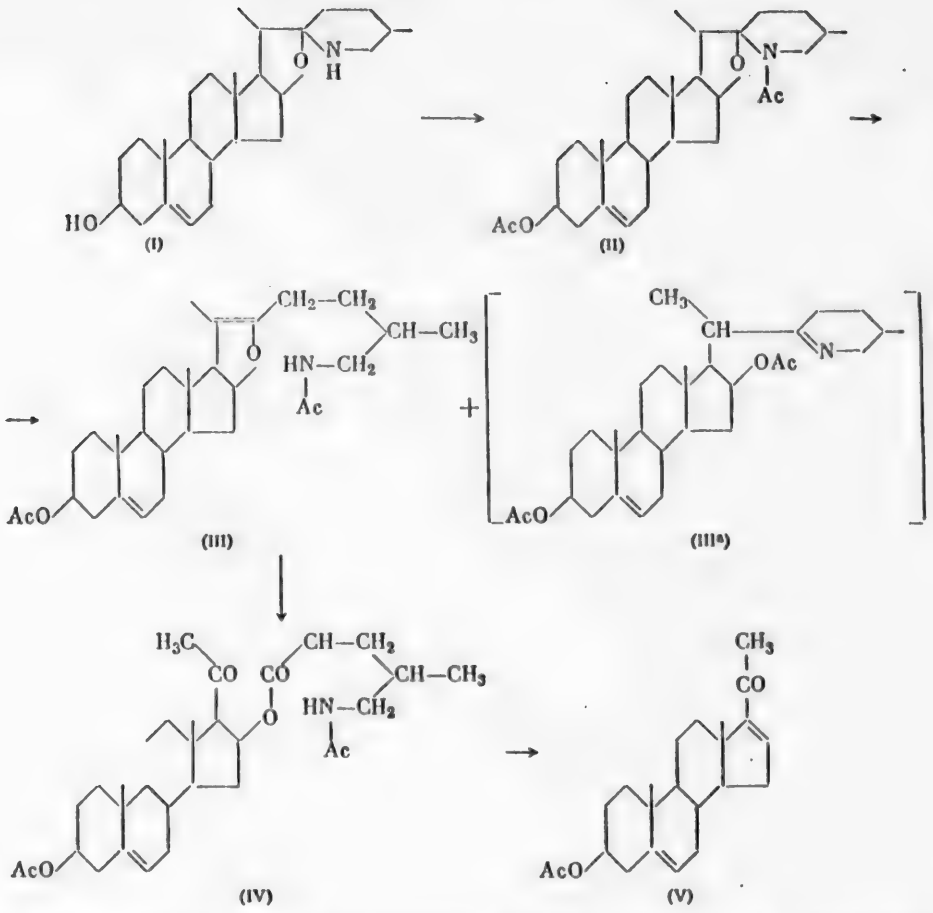
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2062-2067, June, 1960
Original article submitted June 17, 1959

We previously showed that solasodine (I) is a convenient starting material for the synthesis of steroid hormones [1] and described its conversion to progesterone [2] and cortisone [3]. In the present article we present the results of a detailed study of the conversion of solasodine to the acetate of $\Delta^{5,16}$-pregnadienol-3β-one-20 (V). First of all we studied the reaction of solasodine with acetic anhydride in acetic acid in the presence of p-toluenesulfonic acid. As the main intermediate product we isolated substance (III) with m.p. 130-132°, which corresponded in analysis and infrared spectrum to the diacetate of pseudosolasodine, described by Sato, Latham, and Mosettig [4]. A very small amount of substance (IIIa) with m.p. 203-205° and $[\alpha]_D^{20}$ + 51.85° (c 1, $CHCl_3$) was formed as a by-product. Elementary analysis and infrared spectroscopic data indicated that this substance is apparently 3,16-diacetate of pseudosolasodine B, which was also synthesized for the first time by these American investigators, though we obtained it with higher values for the constants. For conclusive demonstration, we prepared the latter by the method of Sato, et al., [4] by treatment of solasodine with acetic anhydride in the presence of anhydrous zinc chloride. After several recrystallizations from methanol and acetone, the 3,16-diacetate of pseudosolasodine B obtained had constants corresponding to those of (IIIa). The infrared spectra of the two substances coincided.

We put forward the hypothesis that the initial product in the conversion of solasodine to the acetate of $\Delta^{5,16}$-pregnadienol-3β-one-20 is not the diacetate of pseudosolasodine (III), but the O,N-diacetate of solasodine (II), described by Briggs and O'Shea [5], which is very rapidly converted to (III) in an acid medium. We acetylated solasodine in the presence of organic bases and Group II metals (magnesium and zinc). However, the best results were given by carbonates of alkali and alkaline earth metals or calcium oxide in toluene with azeotropic distillation of the water, a reaction product formed during acetylation by acetic acid with a metal carbonate or oxide. In actual fact, the O,N-diacetate of solasodine obtained in this way was isomerized into the diacetate of pseudosolasodine (III) by brief heating in acetic acid. Oxidation of (III) with sodium bichromate in acetic acid gave the acetate of Δ^5-16-(δ-acetylamino-γ-methylvaleroxy)-pregnenol-3β-one-20 (IV), which was converted into the acetate of $\Delta^{5,16}$-pregnadienol-3β-one-20 (V) by boiling with acetic acid.

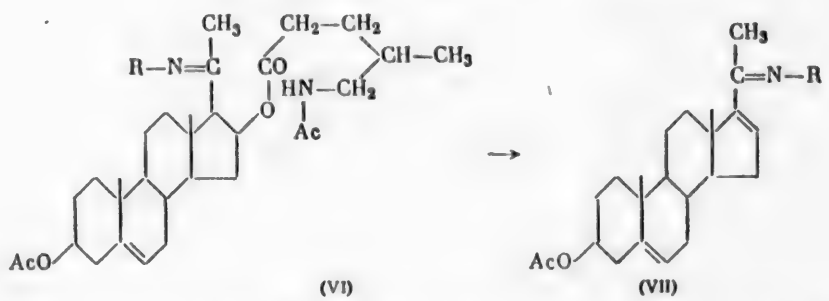
Attempts to prepare the acetate of Δ^5-16-(δ-acetylamino-γ-methylvaleroxy)-pregnenol-3β-one-20 (IV) in a crystalline state have not yet been successful. However, it has been isolated in the form of crystalline derivatives: the oxime (VI; R = OH) and the 2,4-dinitrophenylhydrazone (VI; R = $-NH-$  $-NO_2$).

*Presented at a session of the Section of the Chemistry of Natural Products and Biochemistry of the Eighth Mendeleev Conference on General and Applied Chemistry, March 19, 1959.



The structure of these compounds has been demonstrated by means of ultraviolet and infrared spectra and also by the fact that when heated in acetic acid, they both give the corresponding derivatives of the acetate of

$\Delta^{5,16}$-pregnadienol-3β-one-20 (VII; R = OH and $-NH-C_6H_3(NO_2)_2$, respectively).



Thus, the scheme presented above for the conversion of solasodine to the acetate of $\Delta^{5,16}$-pregnadienol-3β-one-20 may be regarded as demonstrated conclusively.

At the same time, it should be pointed out that when this process was carried out without the isolation of intermediate substances in a pure form and with the use of calcium oxide with azeotropic distillation of the water formed,• in the acetylation of solasodine we reached yields of the acetate of $\Delta^{5,16}$-pregnadienol-3β-one-20 of 60%.

•This method is protected by authors' certificate No. 118499 with priority from March 20, 1958 .

After the present work had been completed, there appeared an article by Bite and Tuzson [6], who reported that they attained the same yield of dehydropregnenolone acetate by using ketene for the acetylation of solasodine. However, the Hungarian chemists did not refer to our previous work on the conversion of solasodine to the acetate of $\Delta^{5,16}$-pregnadienol-3β-one-20, which was published in 1956 [1].

In conclusion we would like to thank Yu. N. Sheinker for carrying out the spectroscopic investigations.

EXPERIMENTAL

The infrared spectra were obtained by means of an IKS-11 spectrometer (NaCl prism). The substances were examined as suspensions in vaseline oil. The ultraviolet spectra were plotted with a SF-4 spectrophotometer.

Acetate of $\Delta^{5,16}$-pregnadienol-3β-one-20 (V). Into a three-necked, round-bottomed flask fitted with a mechanical stirrer with a mercury seal, a dropping funnel, and a reflux condenser with a Dean and Stark head, were placed 50 g of solasodine, 25 g of calcium oxide, and 500 ml of toluene. The mixture was heated to boiling with vigorous stirring and 55 ml acetic anhydride was added to it in one portion. Boiling was continued for 2-3 hr until azeotropic distillation of water ceased. After the reaction mixture had been cooled to 0°, 500 ml of 1.5% acetic acid was added to it gradually. After 15 min, stirring was stopped, the toluene layer separated from the aqueous layer, and the latter extracted 3 times with toluene. The combined toluene extracts were washed with water and the toluene evaporated to dryness in vacuum. The residue was dissolved in 750 ml of 99% acetic acid, and the solution boiled for 15 min and cooled to 20°. Then a solution of 25 g of sodium bichromate in 150 ml of acetic acid was added to it in one portion. The temperature of the reaction mixture rapidly rose to 38-40°. After the mixture had been stirred for 5 min, 7.5 g of anhydrous sodium sulfate, 5 g of activated charcoal, and 60 ml of acetic anhydride were added. The mixture was boiled for 3 hr. The charcoal was removed by filtration and the solution concentrated in vacuum by distillation of 450 ml of acetic acid. With vigorous stirring, 500 ml of water was gradually added to the residue at 25-28°, stirring continued for a further 30 min, and the precipitate of crude acetate of $\Delta^{5,16}$-pregnadienol-3β-one-20 collected by filtration. The latter was washed with 55% acetic acid until the filtrate became colorless and then water, and crystallized in the moist state from 200 ml of alcohol. The yield was 24-24.6 g (58-60%). The m.p. was 72-173°. $[\alpha]^{20}D-36°$ (c 0.9, $CHCl_3$). $E^{1\%}_{cm}$ (ether) 258 at λ 234 mμ.

O,N-Diacetate of solasodine (II). A mixture of 5.0 g of solasodine, 2.5 g of calcium oxide, 5.5 ml of acetic anhydride, and 50 ml of toluene was treated as indicated above. After the acetylation, the inorganic precipitate was removed and washed with dry dichloroethane, and the combined filtrates evaporated to dryness in vacuum. The residue was ground with a small amount of ether and the crystalline precipitate collected by filtration and washed with ether. We obtained 3.67 g of O,N-diacetate of solasodine with m.p. 159-161°. After recrystallization from acetone and ethyl acetate, the substance had m.p. 162-163.5°. $[\alpha]^{20}D-48.5°$ (c 3, $CHCl_3$).

Literature data: m.p. 165-166.5°, $[\alpha]^{20}D-56.3°$ (c 3.41, $CHCl_3$) [5]; m.p. 161-163, $[\alpha]^{20}D-52°$ (c 3, $CHCl_3$) [6].

O,N-Diacetate of pseudosolasodine (III). a) Isolation from reaction mixture. A mixture of 10 g of solasodine, 66 ml of 99% acetic acid, 12 ml of acetic anhydride, and 0.72 g of p-toluenesulfonic acid was boiled for 6 hr. The solvents were removed in vacuum and the residue dissolved in methylene chloride. The solution obtained was washed with cold 5% sodium bicarbonate solution and water and dried with anhydrous magnesium sulfate. The methylene chloride was removed in vacuum, the residue triturated with ether, and the mixture obtained filtered. The precipitate, which was the O,N-diacetate of pseudosolasodine (III), was washed several times with ether. The yield was 7.0 g (61%). The m.p. was 119-122°. After two recrystallizations from ethyl acetate, the product had m.p. 130-132°, $[\alpha]^{20}D-31.3°$ (c 3, $CHCl_3$).

Literature data: m.p. 134-138 [4], m.p. 133-137°, $[\alpha]^{20}D-32°$ (c 3, $CHCl_3$) [6].

Found %: C 74.60, 74.96; H 9.73, 9.43; N 2.88, 2.92. $C_{31}H_{47}O_4N$. Calculated %: C 74.81; H 9.52; N 2.82.

Infrared spectrum: absorption bands in the region of 3232 cm^{-1} (>NH-bond); 1643 cm^{-1} (–CO–N<) 1735 and 1245 cm^{-1} (–O–CO–).

After the separation of (III), the ether solution was evaporated to dryness and the residue recrystallized from acetone. We obtained 0.55 g (4.75%) of the 3,16-diacetate of pseudosolasodine B. The m.p. was 180-182°. After two recrystallizations from methanol, the substance had m.p. 203-205°, $[\alpha]_D^{20}$ + 51.85° (c 1, $CHCl_3$).

Found %: C 75.22; H 9.52; N 2.87. $C_{31}H_{47}O_4N$. Calculated %: C 74.81; H 9.52; N 2.82.

Infrared spectrum: absorption bands in the regions 1732 cm^{-1} (−O−CO−) and 1656 cm^{-1} (>C = N−).

After recrystallization from methanol, acetone, and again methanol, the 3,16-diacetate of pseudosolasodine B, obtained by the method of Sato, et al., [4] had constants agreeing with those presented above. The identity of these substances was confirmed by a comparison of their infrared spectra and an undepressed mixed melting point. Sato [4] reported m.p. 188.5-192.5° and $[\alpha]_D^{20}$ + 46.6° ($CHCl_3$).

b) Isomerization of O,N-diacetate of solasodine. A solution of 1.5 g of O,N-diacetate of solasodine (II) in 25 ml of glacial acetic acid was boiled for 15 min. The solvent was removed in vacuum and the residue mixed with water and collected by filtration. We obtained 1.42 g of the O,N-diacetate of pseudosolasodine (III). After recrystallization from ethyl acetate, the substance had m.p. 130-132°.

Isolation of the acetate of Δ^5-16-(δ-acetylamino-γ-methylvaleroxy)-pregnenol-3β-one-20 (IV). Ten grams of solasodine was converted (without isolation of the intermediate products in a pure state) successively into the O,N-diacetate of solasodine (II) and the O,N-diacetate of pseudosolasodine (III) and the latter was oxidized with sodium bichromate in acetic acid, as described in the preparation of the acetate of $\Delta^{5,16}$-pregnadienol-3β-one-20. When the oxidation was complete, to the reaction mixture was added anhydrous sodium sulfite and the mixture heated for a short time to 80° to remove excess bichromate, cooled, and poured with stirring into ice water. The reaction product was extracted with methylene chloride. The extract was washed with a cold solution of sodium bicarbonate and water and dried with magnesium sulfate. Removal of the solvent yielded 11-11.5 g of (IV) in the form of a vitreous mass.

a) Oxime (VI; R = OH). A mixture of 8.92 g of the oxidation product, 3.60 g of hydroxylamine hydrochloride, and 89 ml of pyridine was allowed to stand at room temperature for 4 days. The solution was poured into water and the precipitate collected, washed with water, and dried. The weight was 6.1 g and the m.p. 115-120°. After recrystallization from carbon tetrachloride and 50% alcohol, the product had m.p. 147-148.5°.

For analysis, the substance was dried at 1 mm and 100° for 5-6 hr.

Found %: C 68.56, 68.57; H 9.20; 8.93; N 5.48, 5.58. $C_{31}H_{48}O_6N_2$. Calculated %: C 68.34; H 8.88; N 5.14.

Infrared spectrum: absorption bands in the regions 3318 cm^{-1} (−NH−OH), 1643 cm^{-1} (>N−C(=O)−), 1732 and 1245 cm^{-1} (−O−CO−).

The ultraviolet spectrum contained no maximum in the region of 240 mμ.

A solution of 0.5 g of the oxime obtained (VI; R = OH) in 15 ml of glacial acetic acid was boiled for 2 hr, then poured into water, and the precipitate collected, washed with water and dried. The weight was 0.29 g. After repeated recrystallization from alcohol, the substance had m.p. 221-222° (in a sealed capillary). This substance did not depress the melting point of an authentic sample of the oxime of the acetate of $\Delta^{5,16}$-pregnadienol-3β-one-20 (VII; R = OH). Their infrared spectra coincided completely.

b) 2,4-Dinitrophenylhydrazone [VI; R = −NH−$C_6H_3(NO_2)_2$]. To a solution of 3.10 g of the oxidation product was added a solution of 1.19 g of 2,4-dinitrophenylhydrazine in a mixture of 14.5 ml of 80% phosphoric acid and 10 ml of alcohol. An orange precipitate of the hydrazone formed immediately. It was collected and washed with alcohol until neutral. The weight was 2.07 g and the m.p. 211-213° (decomp.). After two recrystallizations from alcohol, the product had m.p. 231-232° (decomp.).

Found %: C 62.87; H 7.31; N 10.01. $C_{37}H_{51}O_9N_5$. Calculated %: C 62.70; H 7.21; N 9.89.

Infrared spectrum: absorption bands at 1725 and 1245 cm^{-1} (−O−CO−), 3450 and 3360 cm^{-1} (>NH), 1608 cm^{-1} (>C = N−), 1662 cm^{-1} (−N−C(=O)−).

A mixture of 0.5 g of hydrazone obtained with 15 ml of glacial acetic acid was boiled for 1 hr. The precipitate which formed on cooling was collected with suction and washed with acetic acid and alcohol. The weight was 0.3 g. After recrystallization from ethyl cellosolve, the substance had m.p. 230-231° (decomp.). The substance did not depress the melting point of an authentic sample of the 2,4-dinitrophenylhydrazone of the acetate of $\Delta^{5,16}$-pregnadienol-3β-one-20. The infrared spectra of these substances coincided completely.

SUMMARY

1. A convenient method was developed for preparing the acetate of $\Delta^{5,16}$-pregnadienol-3β-one-20 from solasodine.

2. It was demonstrated experimentally that the conversion of solasodine to the acetate of $\Delta^{5,16}$-pregnadienol-3β-one-20 proceeds through the formation of the O,N-diacetate of solasodine, the O,N-diacetate of pseudosolasodine, and the acetate of Δ^{5}-16-(δ-acetylamino-γ-methylvaleroxy)-pregnenol-3β-one-20.

3. The product of the oxidative cleavage of the O,N-diacetate of pseudosolasodine was isolated for the first time as the oxime and 2,4-dinitrophenylhydrazone.

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STEROID SAPOGENINS

VII. SAPOGENINS OF THE RHIZOMES AND LEAVES OF YUCCA RECURVIFOLIA FROM THE BLACK SEA COAST OF THE CAUCASUS

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2067-2070,
June, 1960
Original article submitted June 12, 1959

In the development of our study of various forms of plants for their steroid sapogenin content, we investigated the rhizomes and leaves of Yucca recurvifolia, grown in Kobuleti (Black Sea coast of the Caucasus) and collected in November (in a dormant state).

According to literature data, smilagenin has been isolated from Y. recurvifolia, grown in America [1], while tigogenin and gitogenin were obtained from plants of the same form, grown in Japan [2]. In a preliminary investigation of the hydrolysis products of rhizomes of our samples of Y. recurvifolia by paper chromatography, four spots of steroid sapogenins were detected: two in the region of monohydroxysapogenins, one in the region of monohydroxyketosapogenins, and another which corresponded to a dihydroxysapogenin in R_f value.

The sapogenins were isolated by various methods. We first used a modification of Wall's method, which we used previously in work with Agave americana [3].

Then, to obtain the complex mixture of sapogenins from the rhizomes of Y. recurvifolia, it seemed interesting to try the method proposed by Rothrock et al. [4] for the rhizomes of Dioscorea barbasco, which contained only one water-soluble saponin. The basic principle of this method is hydrolysis of the saponins directly in the plant material with subsequent extraction of the sapogenins obtained from the plant material residue with ligroin, and we have used it successfully [5] on other forms of the genus Dioscorea, grown both in the USSR (D. caucasica and D. polystachya), and in India (D. deltoidea and containing both water-soluble and water-insoluble saponins.

Our experiments with samples of dioscorea and yuccas showed that the hydrolysis of saponins does not proceed to completion under the conditions described by the American authors, i.e., boiling with 2 N hydrochloric acid for 2 hr, and longer boiling with 2 N hydrochloric acid was necessary, namely for 4.5 hr; boiling for 6 hr was necessary with 1 N hydrochloric acid [5].

As the yield of sapogenins isolated from rhizomes of Y. recurvifolia by the two methods was approximately the same after processing, we tried yet another variant in which carbon tetrachloride was used for extraction of the sapogenins instead of ligroin. In this case, the total of crude sapogenins left after distillation of the solvent from the extracts was much more contaminated with tars than when ligroin was used for the extraction, but the tars were removed very readily by washing with diisopropyl ether.

A comparison of the results of isolating sapogenins by the three variants showed that the yield was of approximately the same order. Thus, in the isolation of the complex mixture of sapogenins, it is also advantageous to hydrolyze the saponins without their preliminary separation from the plant material by boiling the latter with 2 N hydrochloric acid for 4.5 hr, while the sapogenins may be extracted with carbon tetrachloride.

The crude sapogenins obtained from rhizomes of Y. recurvifolia could be separated only by chromatography on alumina with continuous checking of the separate eluates by paper chromatography. As a result, we isolated and characterized four sapogenins: smilagenin, tigogenin, hecogenin, and gitogenin.

The infrared absorption spectra were obtained by our co-workers in the physicochemical laboratory under the direction of Yu. N. Sheinker, whom we would like to thank.

EXPERIMENTAL

Isolation of sapogenins from rhizomes of Y. recurvifolia. A 300-g sample of ground, air-dried rhizomes (particle diameter not more than 2 mm) was boiled with vigorous stirring with 3 liters of aqueous 2 N hydrochloric acid (containing 5% butanol) on a water bath for 4.5 hr. The cooled reaction mass was separated by suction and the residue of unhydrolyzed plant material with sapogenins deposited on it washed twice on the filter with water (250 ml per portion), then transferred to a beaker and stirred with 500 ml of 5% sodium bicarbonate solution, the liquid again sucked off, and the mass washed once again with water (200 ml). After being dried at 80° (to constant weight), the residue weighed 122 g. A portion (58.6 g) of this residue was extracted with ligroin (b.p. 50-70°) in a Soxhlet apparatus for 6 hr. The extract was decolorized with charcoal and the ligroin removed to yield 5.72 g of a light crystalline mixture of sapogenins (3.9% with respect to the plant material taken; crude product). Increasing the extraction time hardly increased the yield. The remaining 63.4 g of residue after hydrolysis was extracted in a Soxhlet apparatus with carbon tetrachloride. After extraction for 6 hr, distillation of the solvent yielded 6.1 g of a solid. Reextraction for 5 hr gave a further 0.29 g of material; the weight of dry residue was not increased by a further increase in the extraction time. After 11 hr, a total of 6.39 g of material was isolated, representing 4.0% of the weight of rhizomes taken. This product was more contaminated with tars than the product obtained by extraction with ligroin. However, washing on the filter with 3-5 ml of diisopropyl ether yielded about 6 g of a light mixture of sapogenins (crude product).

For separation of the sapogenins, 3 g of the crude product was dissolved in 45 ml of dry benzene and chromatographed on 15 times the amount of Al_2O_3. Benzene, ether, and methanol were used successively for elution and 50 ml fractions were collected. The first eight benzene eluates yielded a crystallizable residue (45% of the weight of crude product), which was contaminated with fatty materials. Paper chromatography gave mainly a spot of a monohydroxysapogenin with some of a less polar second monohydroxysapogenin.

The next twelve benzene eluates yielded 0.74 g (24.6%) of a crystalline residue, which corresponded to tigogenin in R_f value. After recrystallization from acetone and methanol, the material had m.p. 199-202°, $[\alpha]^{20}D$ −64.26° (c 1, $CHCl_3$); the acetate had m.p. 201-202°, which corresponds to literature data [6]. The elementary composition of the sapogenin obtained corresponded to the formula $C_{26}H_{46}O_4$, while the infrared spectrum of the acetate corresponded to that of tigogenin acetate [7].

With further washing of the column with benzene and then ether, the eluates contained, in addition to tigogenin, a ketosapogenin, which could be isolated by means of Girard's reagent P. The melting point of the hecogenin obtained was 252-257° [1] and the infrared spectrum of its acetate coincided completely with the known infrared spectrum of hecogenin acetate [7]. The residues obtained after evaporation of methanol eluates (6.66%) were strongly contaminated with tars; according to the results of paper chromatography, they contained a mixture of hecogenin and gitogenin. Washing them with diisopropyl ether yielded 0.04 g of a white crystalline residue. A study of the solubility of this residue in ether under a microscope showed that part, which was considerably more soluble in ether, gave needles; the ether-insoluble crystals had a rhombic form, characteristic of hecogenin. The residual mixture of sapogenins was washed with ether on a filter. After recrystallization from methanol and drying at 65° and 0.1 mm, it melted at 269-271.5°. Its R_f value and the infrared spectrum of its acetate were characteristic of gitogenin and gitogenin acetate, respectively [7].

For identification of the less polar monohydroxysapogenin, the residue after evaporation of the first eight benzene eluates was dissolved in ligroin and chromatographed again on Al_2O_3. Traces of fat were removed by washing with ligroin. Elution with a mixture of ligroin and benzene (1 : 1) yielded a very small amount of a crystalline residue, which had m.p. 183-185° [7] after two recrystallizations from methanol. The infrared spectrum of its acetate was found to be identical with that of smilagenin acetate [7].

On the basis of the different solubilities of the digitonides of tigogenin [8] and smilagenin [9] in alcohol, we separated these sapogenins by means of digitonine. Paper chromatography data showed that this separation was possible.

Isolation of sapogenins from leaves of Y. recurvifolia. Crude sapogenins from the leaves were obtained by hydrolysis of the plant material with subsequent extraction with ligroin under the conditions described above for the rhizomes; the sapogenins were isolated and identified in the same way. The total of crude sapogenins isolated from the leaves represented 1.3% of the raw material. On the basis of the physical constants and mixed melting points with appropriate samples of pure genins, we identified smilagenin, tigogenin, and gitogenin.

SUMMARY

1. From the rhizomes of Yucca recurvifolia grown in Kobuleti on the Black Sea coast of the Caucasus, we isolated 3.9% of a mixture of sapogenins, consisting of four sapogenins, which were identified as tigogenin, smilagenin, hecogenin, and gitogenin.

2. From the leaves of Y. recurvifolia we isolated 1.3% of a mixture of genins, consisting of smilagenin, tigogenin, and gitogenin, which were purified and identified.

3. We demonstrated the possibility of isolating the complex mixture of sapogenins by hydrolysis of the saponins directly in the plant material by boiling for 4.5 hr with 2 N hydrochloric acid containing 5% butanol, with subsequent extraction of the sapogenins with carbon tetrachloride and purification of the total sapogenins obtained from the extract with diisopropyl ether.

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SYNTHESES BASED ON SCLAREOL

II. HYDROCHLORINATION OF SCLAREOL AND DIHYDROSCLAREOL

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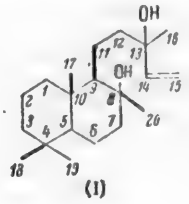
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2070-2073,
June, 1960
Original article submitted May 18, 1959

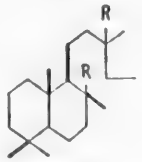
In previous communications [1, 2] it was shown that the reaction of sclareol (I) with hydrogen chloride yields a mixture of monochloro derivatives and sclarenes.

In the present work we describe a new series of experiments for preparing individual halides of sclareol and dihydrosclareol.

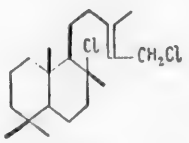
The action of a large excess of hydrogen chloride on a dilute ether solution of sclareol or dihydrosclareol (II) for 40 hr at room temperature yielded crystalline halides. By this method, sclareol gave a 24% yield of the previously undescribed, unsaturated 8,15-dichloro-$\Delta^{13(14)}$-sclarene (III)• with m.p. 114-115°.



(I)



(II) R = OH;
(IV) R = Cl.



(III)

The structure of the halide (III) was confirmed spectroscopically. The infrared spectrum of (III) had a maximum at 832 cm^{-1}, corresponding to a tertiary-secondary double bond > C = CH– [this was not present in the spectrum of dichlorosclarene (IV)]and there were no maxima in the regions of 912 and 980 cm^{-1}, characteristic of a vinyl bond (Fig. 1).

Compound (III) was evidently formed from sclareol as a result of an allyl rearrangement [5].

After (III) had been distilled twice in vacuum, the chlorine content was reduced to 10.95% and remained practically constant during subsequent distillations. This indicates that during vacuum distillation, 8,15-dichloro-$\Delta^{13(14)}$-sclarene loses most readily the chlorine atom in the ring, in analogy with elimination of an acetyl group during distillation of sclareol diacetate [6]. This formed a semicyclic double bond giving an infrared maximum at 891 cm^{-1}, which was absent from the spectrum of the dichloride (III). The formation of the semicyclic double bond confirms the equatorial position of the chlorine atom at C_8 in 8,15-dichloro-$\Delta^{13(14)}$-sclarene and of the hydroxyl group in sclareol.

The mother solutions obtained after separation of (III) were separated chromatographically on alumina. Ligroin, benzene, and ether were used successively for elution.

• The nomenclature we adopted for sclareol derivatives containing 20 carbon atoms is based on the bicyclic hydrocarbon sclarane, the carbon atoms of which are numbered in accordance with the principle adopted for steroids [3]. In the literature [4], the name sclarane is given to a tricyclic hydrocarbon, which in our opinion should be called cyclosclarane.

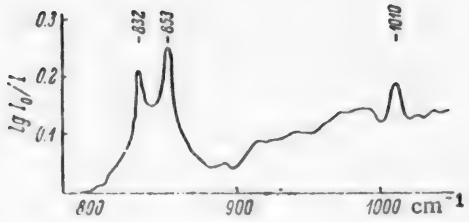


Fig. 1. Infrared spectrum of 8,15-dichloro-$\Delta^{13(14)}$-sclarene (III).

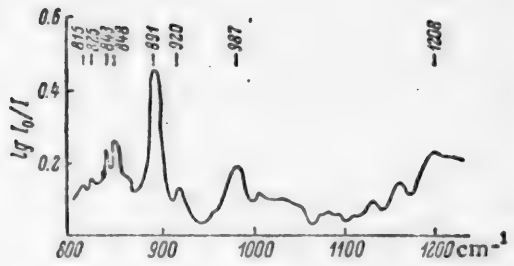


Fig. 2. Infrared spectrum of fraction eluted with ligroin.

The fraction eluted with ligroin was yellowish liquid and contained 12.68% of chlorine. The high chlorine content in comparison with a monochloro derivative of sclareol (11.5%) is apparently explained by the presence of substance (III) in the mixture. After vacuum distillation of the substance, the chlorine content fell to 11.2% due to elimination of one chlorine atom from the dichloride. The distilled substance contained two double bonds and the infrared spectrum showed maxima at 825 (tertiary-secondary double bond > C=CH–), 891 (semicyclic double bond), and also 920 and 897 cm^{-1} (vinyl bond) (Fig. 2). These data agree well with the formula of the monohalide $C_{20}H_{33}Cl$ which we described previously [2].

Redistillation of the fraction eluted with ligroin lead to a fall in the chlorine content to 9.31%. All this indicates that the monohalide contained a tertiary chlorine atom, which is eliminated first of all by heating if it is in the ring (C_8), and after prolonged thermal treatment, if it is in the side chain (C_{13}).

Benzene eluted a very thick yellow liquid, which did not contain chlorine. The infrared spectrum showed maxima at 891 (semicyclic double bond), 917 and 1002 cm^{-1} (vinyl bond) and also a broad absorption band from 1100 to 1200 cm^{-1}, belonging to deformation vibrations of hydroxyl groups. Elementary analysis confirmed the presence of oxygen. It is probable that this fraction consisted of a mixture of oxygen compounds, similar to that obtained by Stoll during the hydrochlorination of (tetramethyl-1,1,6,10-hydroxy-6-decalyl-5)-ethanol [7].

The fraction eluted with ether was not studied in detail. It was a mobile liquid with a definite odor and did not contain chlorine; it had $n^{18}D$ 1.4742.

Hydrochlorination of dihydrosclareol yielded crystalline, saturated 8,13-dichlorosclarane (IV) with the composition $C_{20}H_{36}Cl_2$ and m.p. 131-132°. The yield was 64%. However, the melting point of this substance was 10° above the melting point of dichlorodihydrosclareol obtained by Hosking and Brandt [8] from dihydrosclareol and also from dihydroxymanool.

The mother liquor remaining after separation of the crystalline substance was chromatographed on alumina. Ligroin eluted the bulk of the material, which contained 12.1% of chlorine. After vacuum distillation of the substance, the chlorine content equalled 11.05% and continued to fall during subsequent distillations.

The benzene and ether eluates were not investigated.

EXPERIMENTAL

8,15-Dichloro-$\Delta^{13(14)}$-sclarene (III). A sample of 45 g of sclareol (m.p. 102°) was dissolved in 650 ml of dry ether, into which had been passed 120 g of hydrogen chloride (according to the increase in weight) at −5°. The solution was kept at room temperature (19°) for 40 hr. It was then washed with ice water, sodium carbonate solution, and again with water until chlorine ions were removed completely. After the solution had been dried with sodium sulfate and the ether removed, the residue was recrystallized from acetone. We obtained 12.1 g of a white crystalline substance, which melted at 114-115° after five recrystallizations. A mixed melting point with sclareol was depressed (m.p. 90-93°).

Found %: C 69.22, 69.69; H 10.16, 10.07; Cl 20.30, 20.40. Iodine number 79.7, 76.3. $C_{20}H_{34}Cl_2$. Calculated %: C 69.58; H 9.86; Cl 20.56. Iodine number 73.6.

For determination the behavior of 8,15-dichloro-$\Delta^{13(14)}$-sclarene on alumina, we chromatographed 0.5 g of the substance on 50 g of Al_2O_3 (activity 3.5 according to Brockman). Ligroin (200 ml) eluted 0.32 g (III). It had m.p. 114°.

Vacuum distillation of dichloride (III). A 0.5 g sample of the dichloride was vacuum distilled (168°, 2 mm), when there was considerable elimination of hydrogen chloride (according to an indicator). A pale yellowish liquid was obtained. Found %: Cl 11.96. After a second distillation, the chlorine content was 11.05%. Repeated distillations did not change the halogen content significantly.

Chromatography of mother liquor. A 2 g sample of the oil obtained after separation of (III) was chromatographed on 200 g Al_2O_3 (activity 3.5). Ligroin (550 ml) eluted 0.75 g of a colorless liquid which contained chlorine. Found %: Cl 12.68. During vacuum distillation (155-160°, 2 mm), hydrogen chloride was eliminated with the formation of a monohalide.

$n^{16}D$ 1.5200, d^{16}_4 1.0032, MR_D 93.49; calc. 94.09.

Found %: Cl 11.20. Iodine number 157, 158.5. $C_{20}H_{33}ClF_2$. Calculated %: Cl 11.50. Iodine number 164.5.

The substance obtained was redistilled at 155-162° (2 mm), when the halogen content fell. Found %: Cl 9.31.

Benzene (700 ml) eluted 0.8 g of a very thick yellow liquid which did not contain chlorine or crystallize; it had $n^{18}D$ 1.5198.

Found %: C 81.93; H 11.94.

Diethyl ether (500 ml) eluted a mobile liquid (0.25 g), which had a strong odor, did not contain chlorine, and had $n^{18}D$ 1.4742.

8,13-Dichlorosclarane (IV). A 35 g sample of dihydrosclareol (m.p. 112-113°), obtained by hydrogenation of sclareol over a palladium catalyst, was dissolved in 600 ml of dry ether, into which had been passed 100 g of hydrogen chloride at −5°. The subsequent treatment of the solution was as above. We obtained 25.1 g of a crystalline substance, which melted at 131-132°; after five successive recrystallizations from acetone and ethyl acetate, the substance did not decolorize potassium permanganate solution. A mixed melting point with the starting material was not depressed (m.p. 98-99°).

Found %: C 69.20, 69.26; H 10.42, 10.73; Cl 20.55, 20.38. Iodine number 1.7. $C_{20}H_{36}Cl_2$. Calculated %: C 69.18; H 10.38; Cl 20.44. Iodine number 0.

Chromatography of mother liquor. 1.6 g of the oil obtained after separation of (IV) was chromatographed on 160 g of Al_2O_3 (activity 3.5). Ligroin (350 ml) eluted 0.8 g of a colorless liquid with $n^{18}D$ 1.5112. Found %: Cl 12.10.

Elimination of hydrogen chloride occurred during vacuum distillation (150-165°, 2 mm).

Found %: Cl 11.05. $C_{20}H_{35}Cl$. Calculated %: Cl 11.43. After redistillation.found %: Cl 9.82.

SUMMARY

1. The reaction of sclareol with excess hydrogen chloride yielded the previously undescribed crystalline 8,15-dichloro-$\Delta^{13(14)}$-sclarene $C_{20}H_{34}Cl_2$ and its structure was established. Under the same conditions, dihydrosclareol yielded 8,13-dichlorosclarane $C_{20}H_{36}Cl_2$, which differed in melting point from that described in the literature.

2. During vacuum distillation of 8,15-dichloro-$\Delta^{13(14)}$-sclarene, the chlorine atom in the ring was eliminated more readily than the chlorine atom in the side chain. The formation of a semicyclic double bond indicated the equatorial position of the chlorine atom in the ring.

3. By spectral and chemical analyses it was shown that the ligroin fraction obtained during the chromatography of the mother solution of 8,15-dichloro-$\Delta^{13(14)}$-sclarene was a mixture of the monochlorides described previously.

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SYNTHESES BASED ON SCLAREOL

III. SYNTHESIS OF AMINO DERIVATIVES OF SCLAREOL

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2074-2077,
June, 1960
Original article submitted May 18, 1959

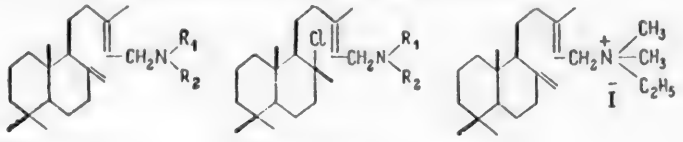
Some quaternary ammonium salts are known to have bactericidal properties [1-4] and are used in a number of cases as disinfectants, sterilizers, and preservers.

We decided to synthesize and test in this respect some quaternary ammonium salts, in particular, sclareol derivatives, and determine the effect of the diterpene radical on the physiological activity of these salts.

The starting materials for the syntheses were 8,15-dichloro-$\Delta^{13(14)}$-sclarene and 8,13-dichlorosclarane, which we obtained previously [5].

The condensation of 8,15-dichloro-$\Delta^{13(14)}$-sclarene with dimethylamine at 70° yielded N-dimethyl-15-amino-$\Delta^{8(20),13(14)}$-sclarodiene (I). The position of the double bonds was demonstrated spectroscopically. The maximum at 830 cm^{-1} in the infrared absorption spectrum corresponds to a secondary–tertiary double bond and those at 895 and 1650 cm^{-1}, to a semicyclic double bond, formed by elimination of an equatorial chlorine atom [6].

The reaction of the same reagents at room temperature in absolute ether gave a chlorine-containing base (II), which decomposed at 80-85° with the liberation of hydrogen chloride.



(I) $R_1 = R_2 = CH_3$; (III) $R_1 = C_2H_5$; $R_2 = H$; (II) $R_1 = R_2 = CH_3$; (IV) $R_1 = C_2H_5$; $R_2 = H$. (V)

When heated with ethylamine, the dichloride formed N-ethyl-15- amino-$\Delta^{8(20),13(14)}$-sclarodiene (III). As in the case with dimethylamine, when the reaction was carried out without heating, the chlorine atom at C_8 was retained and the compound obtained had structure (IV).

By alkylation of (I) and exhaustive methylation of (III) we obtained quaternary ammonium salts of identical composition (V), but with different melting points. This is apparently caused by cis-trans isomerism at the tertiary-secondary double bond.

8,13-Dichlorosclarane behaved very peculiarly during amination. It did not exchange a chlorine atom for an amino group even when heated and was recovered from the reaction; at higher temperatures, a mixture of unsaturated hydrocarbons and chlorides was formed.

As in the case described above, for the chlorine atom at C_8, this is explained by steric hindrance created by axial substituents and the ring residue, as a result of which, replacement of the chlorine by an amino group, which proceeds by an S_N2 mechanism, becomes impossible.

The chlorine atom at C_{13} is blocked by a methyl group; a high expenditure of energy is therefore required in the formation of the intermediate complex in amination. Thus, in both cases, an elimination reaction with the formation of double bonds becomes preferable.

In a preliminary test of the quaternary salts for preserving properties, it was found that doses of 50-100 mg of substance per liter of grape juice were sufficient to prevent fermentation for a long time. Control samples of juice began to become turbid only 2 hr after yeast had been introduced.

EXPERIMENTAL

N-Dimethyl-15-amino-$\Delta^{8(20),\ 13(14)}$-sclarodiene hydrochloride. A mixture of 500 mg of 8,15-dichloro-$\Delta^{13(14)}$-sclarene and 4 ml of a saturated alcohol solution of dimethylamine was heated for 3 hr at 70° in a stainless steel autoclave. After the mixture had stood for 12 hr, the excess dimethylamine and solvent were removed in vacuum. The residue was extracted with ether. The combined ether solutions were washed with water and dried with sodium sulfate. A stream of hydrogen chloride was passed into the dried ether solution until precipitation was complete and then the ether was evaporated to dryness and the residue recrystallized from acetone. We obtained 430 mg of a white, finely crystalline substance with m.p. 197-198° (decomp.).

Found %: C 74.98, 74.67; H 11.61, 11.53; N 3.88, 3.94; Cl 10.27, 10.27. $C_{22}H_{39}N \cdot HCl$. Calculated %: C 74.68; H 11.32; Cl 10.04; N 3.96.

When a sample of the hydrochloride was hydrogenated over a palladium catalyst at room temperature, in 3 hr it absorbed 1.24 ml of H_2 (instead of 1.31 ml, calculated for 2 double bonds).

N-Dimethyl-15-amino-$\Delta^{8(20),\ 13(14)}$-sclarodiene (I). 250 mg of N-dimethyl-15-amino-$\Delta^{8(20),\ 13(14)}$-sclarodiene hydrochloride was shaken with 10 ml of 10% alkali solution. The base was extracted with ether. The ether solution was washed with water and dried, and the ether removed. We obtained 210 mg of a yellow liquid ($n^{18}D$ 1.5105), which decomposed when vacuum distilled (0.1 mm).

Found %: N 4.22, 4.26. $C_{22}H_{39}N$. Calculated %: N 4.42.

8-Chloro-N-dimethyl-15-amino-$\Delta^{13(14)}$-sclarene hydrochloride. A solution of 345 mg of 8,15-dichloro-$\Delta^{13(14)}$-sclarene in 5 ml of absolute ether was saturated with dimethylamine. A precipitate of dimethylamine hydrochloride began to form after a few minites. After the mixture had stood for 20 hr, the precipitate was separated from the solution by decantation. The ether and excess dimethylamine were removed by distillation and the residue extracted with ether. After the ether solution had been washed and dried, a stream of hydrogen chloride was passed in until precipitation was complete. The hydrochloride was collected and recrystallized three times from ether with a little alcohol and then dried over P_2O_5. We obtained 350 mg of a substance which did not have a sharp melting point. At 85-90° it began to decompose with the liberation of hydrogen chloride (according to an indicator).

Found %: C 67.89, 67.98; H 10.60, 10.70; N 3.44, 3.28; Cl 18.15, 18.18. $C_{22}H_{40}NCl \cdot HCl$. Calculated %: C 67.69; H 10.51; N 3.59; Cl 18.21.

Treatment of the hydrochloride with alkali solution as described above and subsequent extraction with ether yielded 8-chloro-N-dimethyl-15-amino-$\Delta^{13(14)}$-sclarene (II) as a yellow liquid, which decomposed during distillation with the liberation of hydrogen chloride.

Iodoethylate (V). 100 mg of base (I) was dissolved in 2 ml of acetone and 1 ml of freshly distilled ethyl iodide added. The mixture was boiled under reflux on a water bath for 1.5 hr and left to stand for a day. The acetone and excess ethyl iodide were then removed. The solid residue was precipitated from acetone with ether and recrystallized from water. We obtained 100 mg of substance with m.p. 182-183°.

Found %: C 60.88, 60.75; H 9.35, 9.22; I 26.73, 26.81. $[C_{24}H_{44}N]^+I^-$. Calculated %: C 60.88; H 9.30; I 26.85.

N-Ethyl-15-amino-$\Delta^{8(20),\ 13(14)}$-sclarodiene hydrochloride. A mixture of 800 mg of 8,15-dichloro-$\Delta^{13(14)}$-sclarene and 3 ml of ethylamine was heated for 3 hr at 70° in an autoclave. After the mixture had stood for 15 hr, the ethylamine was removed and the residue treated as described above. The precipitate obtained after hydrogen chloride had been passed into the solution was recrystallized from 35% alcohol. We obtained 680 mg of lustrous scales with m.p. 184°.

Found %: C 74.96, 74.99; H 11.41, 11.51; N 3.90, 3.94; Cl 9.96, 9.60. $C_{22}H_{39}N \cdot HCl$. Calculated %: C 74.68; H 11.32; N 3.96; Cl 10.04.

When hydrogenated over a palladium catalyst, the substance absorbed 1.39 ml of H_2 (instead of 1.31 ml, calculated for 2 double bonds).

N-Ethyl-15-amino-$\Delta^{8(20),\ 13(14)}$-sclarodiene (III). The hydrochloride (350 mg) was treated with alkali as described above. We obtained 250 mg of liquid with $n^{17}D$ 1.5152.

Found %: N 4.35, 4.26. $C_{22}H_{39}N$. Calculated %: N 4.42.

8-Chloro-N-ethyl-15-amino-$\Delta^{13(14)}$-sclarene hydrochloride. To a solution of 345 mg of 8,15-dichloro-$\Delta^{13(14)}$sclarene in 4 ml of absolute ether was added 0.7 ml of ethylamine. After 40 hr, the solution was treated as described for the hydrochloride of base (I). Recrystallization from a mixture of ether and alcohol yielded 300 mg of a finely crystalline substance which did not have a sharp melting point. It began to decompose at 85-90°.

Found %: C 67.01, 67.17; H 10.60, 10.69; N 3.35, 3.49, Cl 18.51, 18.65. $C_{22}H_{40}NCl \cdot HCl$. Calculated %: C 67.69; H 10.51; N 3.59; Cl 18.21.

Extraction with ether from an alkaline solution yielded 8-chloro-N-ethyl-15-amino-$\Delta^{13(14)}$-sclarene (IV), which decomposed on heating with the liberation of hydrogen chloride.

Exhaustive methylation of N-ethyl-15-amino-$\Delta^{8(20),\ 13(14)}$-sclarodiene. A mixture of 200 mg of base, 2 ml of acetone, and 1 ml of methyl iodide was heated under reflux for 1.5 hr on a water bath. After 15 hr, the acetone and excess methyl iodide were removed by distillation. The residue was shaken with 10 ml of 10% alkali and extracted with ether. The ether extracts were washed with water and dried and the ether was removed. The oily residue was remethylated with methyl iodide under the same conditions. Removal of the excess methyl iodide and the acetone left a dark yellow oil, which had m.p. 158-159° after reprecipitation from acetone with ether, recrystallization from water, and drying over P_2O_5.

Found %: C 60.75, 60.94; H 9.38, 9.47; I 26.44, 26.78. $[C_{24}H_{44}N]^+I^-$. Calculated %: C 60.88; H 9.30; I 26.85.

Reaction of 8,13-dichlorosclarane with ethylamine. A mixture of 350 mg of 8,13-dichlorosclarane and 3 ml of ethylamine was heated at 75° for 8 hr in an autoclave. After 48 hr, the ethylamine was removed by distillation and the residue extracted with ether. Hydrogen chloride was passed into the dry ether solution for 15 min. After 12 hr, the solution was separated from the very small amount of oily material. Evaporation of the ether yielded 340 mg of a crystalline substance, which did not contain nitrogen, had m.p. 130° (from ethanol), and did not depress the melting point of the starting 8,13-dichlorosclarane.

If the contents of the autoclave were heated for 20 hr at 125-130° and then processed by the method described above, instead of the crystalline substance, we obtained 300 mg of a yellowish liquid. When this was chromatographed on 30 g of Al_2O_3, ligroin eluted 220 mg of liquid, which gave a qualitative reaction for chlorine, but no reaction for nitrogen. The liquid was vacuum distilled.

Found %: Cl 7.50. $C_{20}H_{33}Cl$. Calculated %: Cl 11.50.

The infrared spectrum had maxima at 820, 890, and 1640 cm^{-1}, corresponding to $> C = CH-$ and $> C = CH_2$.

SUMMARY

1. Condensation of 8,15-dichloro-$\Delta^{13(14)}$-sclarene with dimethylamine and ethylamine yielded new diterpene bases. We also prepared the quaternary ammonium salts of these bases, which had bactericidal properties.

2. 8,13-Dichlorosclarane does not condense with amines. The elimination of hydrogen chloride occurs in this case.

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PYRROLIZIDINE ALKALOIDS

I. SYNTHESIS OF 1-HYDROXYMETHYLPYRROLIZIDINE (DL-TRACHELANTHAMIDINE)

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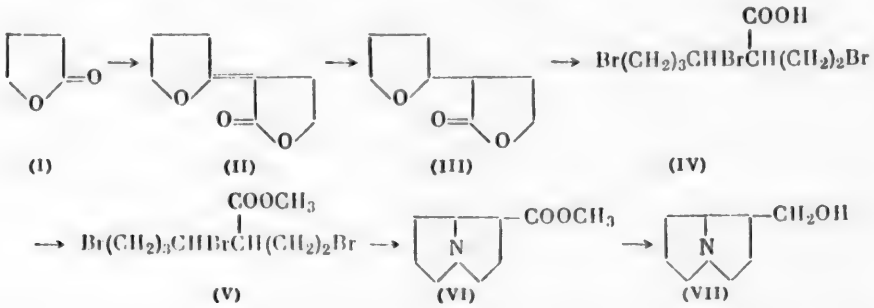
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2077-2082,
June, 1960
Original article submitted June 7, 1959

Many alkaloids containing a pyrrolizidine nucleus have been isolated and the number of representatives of this class increases continuously [1, 2]. Despite the fact that the structure of many alkaloids of this group has been established quite unequivocally, no complete synthesis of a pyrrolizidine alkaloid has been achieved up to now.• This is primarily connected with the fact that there are no suitable methods for synthesizing pyrrolizidine amino alcohols, which form the basis of these alkaloids. Leonard and Felley [3] made an attempt to prepare the simplest of the amino alcohols, namely, 1-hydroxymethylpyrrolizidine, by reductive cyclization of diethyl β-acetoxymethyl-γ-nitropimelate. However, the authors were only able to isolate traces of the given compound as the picrate so that this method cannot be considered satisfactory.

We have now developed a convenient method of synthesizing the simplest amino alcohol of the pyrrolizidine series, namely, 1-hydroxymethylpyrrolizidine (DL-trachelanthamidine), the D-form of which is the natural alkaloid laburnine, while the L-form is present in the alkaloids trachelanthamine and viridiflorine.

The synthesis was carried out according to the following scheme:



The starting material was 3-(2'-tetrahydrofuranylidine)-butyrolactone (II), which is readily obtained by condensation of butyrolactone (I) in the presence of sodium alcoholate by the method of Fittig and Strom [4], which was worked out in detail by Spencer and Wright [5].

For hydrogenating systems similar to (II), Reppe and his co-workers [6] recommended the use of a nickel catalyst at 100° and 200 atm, but no detailed procedure for the preparation of 3-(2'-tetrahydrofuryl)-butyrolactone (III) was given.

•When the present work was complete, there appeared an article by Czech chemists on the synthesis of 1-hydroxymethylpyrrolizidine [22].

We studied this stage of the synthesis in detail and showed that good results are obtained by hydrogenation of (II) over Raney nickel at room temperature and 6 atm. The yield of (III) was 50%. Together with (III), we obtained a considerable amount of high-boiling products, which were probably obtained as a result of hydrogenolysis of the tetrahydrofuran ring with the semicyclic bond, which is similar in character to a vinyl ether [7]. It is interesting to note that attempts to hydrogenate (II) to (III) over platinum or palladium on barium sulfate under the same conditions gave a negative result.

When 3-(2'-tetrahydrofuryl)-butyrolactone (III) was heated in a sealed ampule at 100° with fuming hydrobromic acid, in addition to the tetrahydrofuran ring [8-10], the lactone ring was opened to form the tribromo acid (IV), which was treated with thionyl chloride and methanol [11] without purification to give the methyl ether (V). The latter was a heavy, dark oil, which decomposed during attempts at distillation (cf. [12]); it was therefore used without purification.

It was cyclized to pyrrolizidinecarboxylic acid by heating with a methanol solution of ammonia at 130-140° by the method of Prelog, et al. [13, 14], which was extended to the preparation of pyrrolizidine bases [8-10, 12, 15].

The difference between (V) and tribromides used previously for cyclization was the presence of a bromine atom in a position β to a carbomethoxyl group.

The comparatively low yield of cyclization products in our case is probably explained by the elimination of hydrogen bromide from the β-bromo ester under the action of ammonia with the formation of some unsaturated substances.

As there was also ammonolysis of the ester group under the drastic cyclization conditions, for conversion of the pyrrolizidinecarbonamide formed to its ester, the reaction mixture was treated with methanolic hydrogen chloride and then thionyl chloride and methanol. This gave methyl pyrrolizidine-1-carboxylate (VI) in 30% yield [calculated on (III)] and this was identified as the picrate.

The last stage of the synthesis, i.e., reduction of the ester (VI), was achieved by the action of lithium aluminum hydride in ether. The reaction proceeded smoothly and gave 1-hydroxymethylpyrrolizidine (VII) in 56% yield.

Thus, the scheme presented for the synthesis of 1-hydroxymethylpyrrolizidine is convenient from the preparative point of view as it starts from a readily accessible material and gives satisfactory yields at all stages.

As the methyl pyrrolizidine-1-carboxylate and 1-hydroxymethylpyrrolizidine have two asymmetric atoms, the synthesis could form two racemates corresponding to the configurations of heliotridan and pseudoheliotridan.

Chromatographic investigation of (VI) showed that despite the sharp boiling point (over a range of 0.5°) and the good analysis result, the cyclization product obtained was a mixture of two substances. Only a picrate with m.p. 140-142° could be isolated in a pure form. As will be shown below, the contaminant was not the second racemate of (VI).

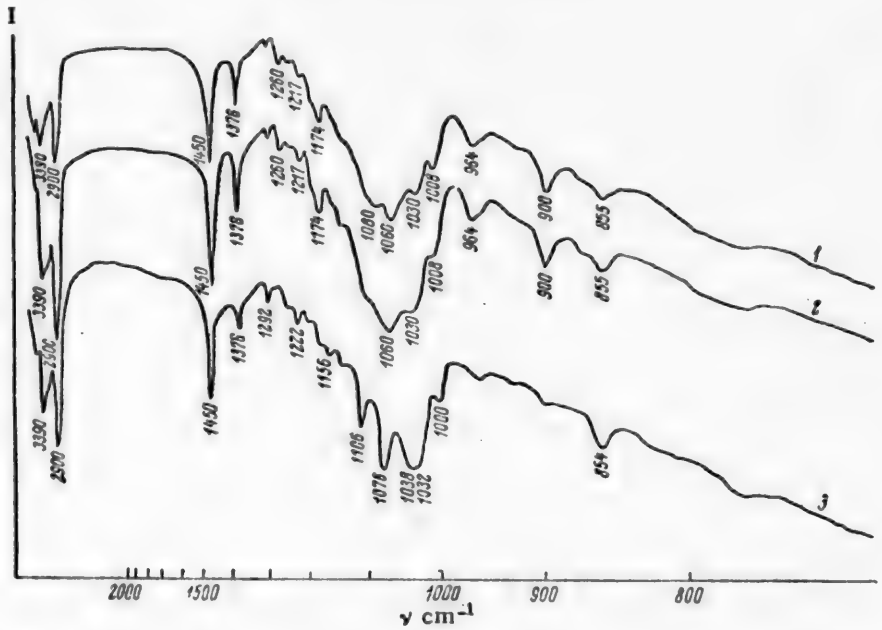
Careful distillation of the reduction products of (VI) yielded two fractions: 1st b.p. 70-75° (0.8-1 mm); 2nd b.p. 87-90° (0.8-1 mm). In a chromatographic comparison of these fractions with trachelanthamidine and lindelofidine it was found that the required product was the fraction with an R_f value of 0.365. The 1-hydroxymethylpyrrolizidine obtained gave a picrate with m.p. 172-173°. No picrates with other melting points were isolated.

Thus, the cyclization of the tribromo ester (V) proceeded stereospecifically and the impurity present in the ester (VI) was not the second racemate. The melting point of the picrate we obtained from (VII) corresponded to the melting point given for DL-trachelanthamidine by Leonard and Felley [3]• and also the melting points of trachelanthamidine and laburnine picrates [16, 17], but differed from the melting point of lindelofidine picrate [18], a sample of which had m.p. 191-193°.

• The authors did not demonstrate the stereochemical structure of the picrate they obtained. They assigned it to the pseudoheliotridan system on the basis of a comparison of its melting point with that of the picrate of natural trachelanthamidine.

The picrate we obtained did not depress the melting point of DL-trachelanthamidine picrate, which we prepared from equal amounts of trachelanthamidine and laburnine picrates (m.p. 172-173°), but gave some depression when mixed with DL-isoretronecanol, obtained from equal amounts of L-isoretronecanol and lindelofidine picrates (m.p. 168-170°). From this it followed that we obtained DL-trachelanthamidine.

For a final determination of the stereochemical structure of the 1-hydroxymethylpyrrolizidine we obtained, the infrared absorption spectra• of trachelanthamidine, lindelofidine, and synthetic 1-hydroxymethylpyrrolizidine (see figure) were plotted. The spectrum of synthetic 1-hydroxymethylpyrrolizidine was found to be identical with that of L-trachelanthamidine but differed from that of lindelofidine.



Infrared absorption spectra. 1) Lindelofidine; 2) 1-hydroxymethylpyrrolizidine; 3) trachelanthamidine.

From the combination of these data, it could be concluded that the 1-hydroxymethylpyrrolizidine obtained was identical with DL-trachelanthamidine.

Consequently, in our case the cyclization led to a pseudoheliotridan structure, as has been observed in other syntheses of pyrrolizidine systems, carried out by different [3, 19] or similar methods [20].

It should be noted that since the pseudoheliotridan system was formed predominantly in all cases (despite differences in the methods used to prepare it), in all probability, the stereochemical similarity of the results obtained should be ascribed not so much to stereochemical direction of closure of the pyrrolizidine ring as to the higher stability of the pseudoheliotridan system in comparison with the heliotridan system (cf. [21]).

The synthesis of 1-hydroxymethylpyrrolizidine by the method we proposed is quite convenient and opens up a route to the synthesis of some pyrrolizidine alkaloids. Work is continuing in this direction.

We are very grateful to A. P. Arendaruk and S. A. Labenskii for providing samples of natural amino alcohols.

EXPERIMENTAL

3-(2'-Tetrahydrofuryl)-butyrolactone (III). Ten grams of "dibutyrolactone" (II) (m.p. 85-87°) in 100 ml of anhydrous methanol was hydrogenated at room temperature and 6 atm over Raney nickel. After 2 hr, about

• The spectral investigations were carried out by V. G. Vinokurov. The spectra were plotted on an IKS-12 instrument with a thin layer and an NaCl prism.

2.1 liters of hydrogen had been absorbed. The catalyst was removed by filtration, the methanol evaporated, the residue distilled, and a fraction with b.p. 92-95° (1-1.5 mm) collected. We obtained 5.2 g (52%) of the dihydro compound (III) as a colorless, mobile liquid, which, after redistillation, had b.p. 78-79° (0.8-1 mm), d^{20}_4 1.1692, $n^{20}D$ 1.4759.

Found %: C 61.94; H 7.93. $C_8H_{12}O_3$. Calculated %: C 61.52; H 7.74.

1,4,7-Tribromo-3-carbomethoxyheptane (V). A solution of 10 g of 3-(2'-tetrahydrofuryl-butyrolactone (III) in 125 ml of hydrobromic acid (d 1.79) was heated in a sealed ampule at 100° for 5 hr. The heavy, colored oil formed was extracted with benzene. The extracts were washed with water and dried with magnesium sulfate. Removal of the benzene yielded 23.5 g of oily 1,4,7-tribromo-3-carboxyheptane (IV), which was dissolved in 60 ml of anhydrous methanol and 6.5 ml of thionyl chloride added with stirring and cooling. The solution obtained was kept at room temperature for 48 hr, the methanol removed by distillation, and the residue evaporated with dry benzene. We obtained 22.5 g of 1,4,7-tribromo-3-carbomethoxyheptane (V) as a viscous brown oil, which was insoluble in water and decomposed during attempts to distill it.

Methyl pyrrolizidine-1-carboxylate (VI). A solution of 22.5 g of unpurified 1,4,7-tribromo-3-carbomethoxyheptane (V) in 175 ml of anhydrous methanol was saturated with ammonia at 0°. The solution obtained was heated in an autoclave at 130-140° for 4 hr. The reaction mixture was evaporated to small volume and then anhydrous methanol added to give a total volume of 150 ml. The solution obtained was saturated with hydrogen chloride and boiled for 3 hr. The methanol was removed by distillation and the residue evaporated with dry toluene. The oil obtained was dissolved in 60 ml of anhydrous methanol and 6.5 ml of thionyl chloride added with stirring and cooling. The reaction mixture was stirred at 25-30° for 5 hr. The precipitate was collected and washed with anhydrous methanol. The filtrate was evaporated, the residue dissolved in 10 ml of cold water and made alkaline with potassium carbonate, and the product extracted with ether. The ether solution was dried with sodium sulfate, the ether evaporated, the residue distilled, and a fraction with b.p. 79-80° (4 mm) collected. We obtained 3.5 g of (VI) [32% calculated on (III)] as a colorless, mobile liquid with an amine odor, which had b.p. 57° (0.8-1 mm), d^{20}_4 1.0706, $n^{20}D$ 1.4770.

Found %: C 64.20; H 9.25; N 8.42. $C_9H_{15}O_2N$. Calculated %: C 63.87; H 8.94; N 8.27.

The picrate was obtained by mixing an alcohol solution of methyl pyrrolizidine-1-carboxylate with an alcohol solution of picric acid, saturated in the cold. Three recrystallizations from alcohol yielded the substance as yellow, lustrous needles with m.p. 140-142°.

Found %: N 14.15. $C_{15}H_{18}O_9N_4$. Calculated %: N 14.07.

1-Hydroxymethylpyrrolizidine (DL-trachelanthamidine) (VII). A solution of 3.2 g of methyl pyrrolizidine-1-carboxylate (VI) in 50 ml of absolute ether was added dropwise over a period of 30 min to a stirred solution of 1.6 g of lithium aluminum hydride in 55 ml of ether. The reaction mixture was stirred at the boiling point for 1.5 hr and then with careful cooling it was decomposed successively with 2 ml of water, 1 ml of 20% sodium hydroxide, 6 ml of water, and 7 ml of 40% sodium hydroxide. The product was extracted carefully with ether. The ether solution was dried with potassium carbonate, the ether evaporated, the residue vacuum distilled, and a fraction with b.p. 85-90° (0.8-1 mm) collected. The yield was 1.45 g (56%). Redistillation yielded a colorless, viscous oil with b.p. 88-90° (0.8-1 mm), d^{20}_4 1.0458, $n^{20}D$ 1.4988, R_f 0.365 (ascending chromatogram, Whatman No. 1, 16 hr, moving phase: butanol–acetic acid–water 4 : 1 : 5, development by iodine vapor).*

Found %: C 68.39; H 10.96; N 10.01. $C_8H_{15}ON$. Calculated %: C 68.03; H 10.71; N 9.93.

The picrate was obtained by mixing ether solutions of 1-hydroxymethylpyrrolizidine in picric acid. Three recrystallizations from alcohol yielded lustrous yellow platelets with m.p. 172-173°.

Found %: N 15.12. $C_{14}H_{18}O_8N_4$. Calculated %: N 15.13.

From the mother solutions obtained after recrystallization we isolated a picrate with the same melting point. A mixture with the picrate of DL-trachelanthamidine (obtained from equal amounts of the picrates of

*Under the same conditions, trachelanthamidine had R_f 0.364 and lindelofidine had R_f 0.362.

L-trachelanthamidine and laburnine) melted at 172-173°. A mixture with the picrate of DL-isoretronecanol (obtained from equal amounts of the picrates of L-isoretronecanol and lindelofidine) melted at 168-170°.

SUMMARY

A method was developed for synthesizing 1-hydroxymethylpyrrolizidine, which was found to be DL-trachelanthamidine.

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GLYCOSIDES OF THE PLANT APOCYNUM ANDROSAEMIFOLIUM L.

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2082-2085,
June, 1960
Original article submitted June 18, 1959

As was shown by Stoll and Kreis [1], most cardiac glycosides are present in plants as more complex compounds than those which are isolated. During the extraction of the plant material, the specific enzymes which accompany glycosides in plants usually hydrolyze the sugar-rich genuine glycosides to less complex compounds, the bulk of which are attached to only one sugar molecule. Consequently, if a monoglycoside is detected in some plant, there are grounds for considering that under certain conditions, it would be possible to isolate from this plant a glycoside containing two or more sugar molecules.

The purpose of the present investigation was to determine the nature of the original polyglycosides of Apocynum androsaemifolium L.• (flytrap) fam. Apocynaceae. Previous investigators [3, 4] have detected the glycoside cymarin in the roots of this plant. Starting from the premise that cymarin is the enzymic cleavage product of the diglycoside k-strophanthin-β [5] and in view of the fact that this always accompanies it in Strophanthus kombe, we concluded that there is a possibility of finding k-strophanthin-β in flytrap also.

Two parallel experiments were carried out first. In the first of these, the glycosides were extracted under conditions where the action of hydrolyzing agents was excluded as far as possible. In the other experiment, the plant material was subjected to fermentation. The extracts were treated in the usual way and put onto chromatography paper. In the first experiment, the chromatogram showed spots corresponding to k-strophanthin-β and cymarin; as was expected, in the second experiment, only the spot of cymarin remained.

k-Strophanthin-β was isolated in a crystalline state under conditions where the action of enzymes was prevented as far as possible. All operations, including the distillation of solvents, were carried out at temperatures below 40-45°. The crystalline diglycoside isolated from the roots of A. androsaemifolium had m.p. 196-198° and $[\alpha]_D$ + 26.7° (in methanol). The lethal dose in tests on cats was 0.147 mg per kg of animal weight. The diglycoside was identified with an authentic sample of k-strophanthin-β from seeds of S. kombe and also from the R_f value on an ascending chromatogram, color reactions, and by comparison of the hydrolysis products.

Cymarin is found in A. venetum [3, 4] and A. cannabinum [3, 4, 6] in addition to A. androsaemifolium in plants of the genus Apocynum. k-Strophanthin-β evidently accompanies cymarin in these plants also.

EXPERIMENTAL

The subject of the investigation was the roots of a plant grown in the experimental section of the Botanical Gardens of the Academy of Sciences, Uzbek SSR.•• The raw material was collected in autumn when the roots accumulate the maximum amount of glycoside [6] and had an activity corresponding to 210 frog units per g of plant material.

•According to the botanical system adopted now in the USSR [2], this plant should be called Trachomitum androsaemifolium, but as it is not indigenous, we have used the old name under which it was studied by previous authors.

••The authors would like to thank K. Kh. Khodzhaev for supplying the raw material.

Preliminary experiments. a) A 100-g sample of dry, ground roots was extracted 6 times with cold methanol. The methanol extract was concentrated to 50 ml in vacuum, filtered, and diluted with an equal volume of water. The ballast substances were precipitated with a solution of 20 g of lead acetate in 20 ml of water. The excess lead ions were removed by addition of an aqueous solution of sodium sulfate until precipitation was complete and then the extract was again concentrated to 25 ml. A few drops of the extract thus obtained were put onto chromatography paper and analyzed in the usual way (system toluene—butanol—water, 1 : 1 : 1). Development with Raymond's reagent showed two spots: one intensely colored, one at the level of k-strophanthin-β and a less marked spot at the level of cymarin (see figure).

b) A 200-g sample of ground roots was stirred with 600 ml of water and then left in a thermostat at 37° for 3 days. The water was squeezed out of the raw material, which was extracted 6 times with hot methanol. The methanol extract was concentrated to 500 ml and mixed with the water extract, pressed out of the raw material after fermentation. The ballast substances were precipitated with lead acetate, which was added until precipitation was complete. The excess lead ions were removed with sodium sulfate and the solution was concentrated to 200 ml in vacuum. On a paper chromatogram, a sample of this extract gave a single spot corresponding to cymarin. The extract was then extracted several times with equal volumes of ether and then chloroform. When concentrated, the ether extract crystallized. The crystals were collected and recrystallized from water when they had m.p. 114-115°. The properties of this substance corresponded to acetovanillone (apocynin) [7].

Found %: C 65.01, 65.22; H 6.23, 6.19. $C_9H_{10}O_3$. Calculated %: C 65.05; H 6.06.

Paper chromatogram. 1) Purified extract of roots that had not fermented; 2) purified extract of roots that had fermented; 3) k-strophanthin-β; 4) cymarin.

The chloroform solution was evaporated to dryness in vacuum. The residue was ground to a powder and dissolved in methanol and slow evaporation of the solution in air yielded crystals (220 mg). Two recrystallizations from methanol yielded 100 mg of substance with m.p. 148°, which was identical with cymarin.

Isolation of k-strophanthin-β. A 1.8 kg sample of dry raw material was extracted and treated as described in experiment (a). After precipitation of the excess lead ions, the extract was concentrated to 400 ml and extracted in turn (4 times) with equal volumes of ether, chloroform, and then a mixture of chloroform and ethanol such that the volume ratio of water, chloroform, and ethanol during the extraction was kept at 2 : 2 : 1.

The ether-soluble fraction of substances was not studied in detail. Paper chromatography showed that it contained a small amount of cymarin. Concentration of the chloroform extract gave 2.5 g of residue. Further treatment of this fraction yielded 0.6 g of cymarin. The chloroform-ethanol fraction was evaporated to dryness in vacuum. We obtained 4.5 g of a light, resinous mass which contained k-strophanthin-β. This mass was dissolved in 100 ml of water and extracted in turn with chloroform and a mixture of chloroform and ethanol (in the same ratio as the first time). The dry residue obtained from the last chloroform—ethanol extract was dissolved in ethanol; the solution was passed through a column with 20 g of alumina and evaporated to dryness and the residue dissolved in water. When the water was evaporated slowly over many days, the aqueous solution deposited crystalline k-strophanthin-β (1.2 g). The latter was purified by recrystallization from alcohol and ether.

The diglycoside from flytrap was a crystalline powder with an intensely bitter taste. It was readily soluble in methanol and ethanol, difficultly so in cold water and chloroform, and practically insoluble in diethyl ether and ligroin. The glycoside gave positive Legal, Liebermann, Balet, Raymond, and Kedde reactions. The Keller—Kiliani reaction was negative. With concentrated sulfuric acid, the substance gave the emerald green color characteristic of k-strophanthin-β.

The glycoside crystallized with a variable amount of water, one molecule of which was firmly held, even after drying in vacuum at 105-110°. With slow heating, a sample of this glycoside had m.p. 196-198°. Melting was accompanied by liberation of gas bubbles, which were evidently water vapor. With rapid heating, the melting point sometimes rose to 213-215° and the substance had $[\alpha]_D$ + 26.7° (c 1.40, methanol).

Found %: C 58.96, 58.97; H 8.01, 7.96. $C_{36}H_{51}O_{14} \cdot H_2O$. Calculated %: C 59.33; H 7.74.

A 200 mg sample of k-strophanthin-β was hydrolyzed with an enzyme mass obtained by extracting flytrap roots with water. The usual processing yielded 130 mg of crystalline compound with m.p. 148°. A mixed melting point with cymarin was not depressed. In contrast to k-strophanthin-β, the compound obtained gave a positive Keller–Kiliani reaction.

Found %: C 63.85, 63.75; H 8.26, 8.10; OCH_3 9.14, 9.53. $C_{30}H_{44}O_9 \cdot CH_3OH$. Calculated %: C 64.12; H 8.33; 2 OCH_3 9.36.

Acid hydrolysis of k-strophanthin-β and the cymarin obtained from it gave strophanthidin with m.p. 176-177°.

SUMMARY

Extraction of the roots of the plant Apocynum androsaemifolium under conditions where the action of fermentative agents was excluded as much as possible yielded cymarin and also a diglycoside which was completely identical with k-strophanthin-β that has been found previously in seeds of Strophanthus kombe.

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SYNTHESIS OF THE NATURAL ALKALOID (+)-CINCHONAMINE

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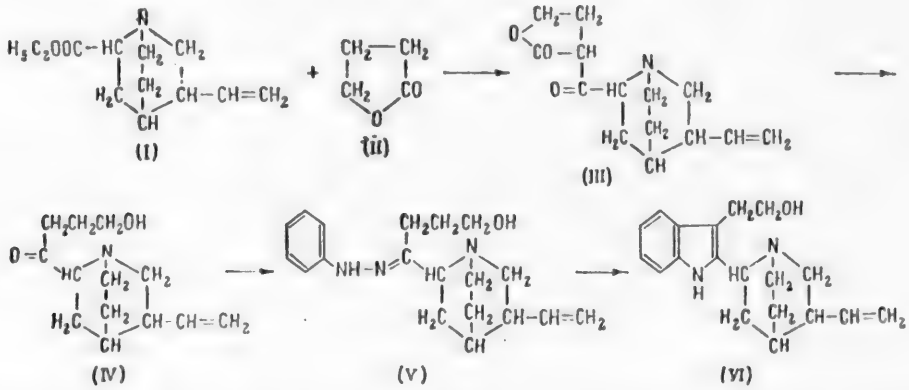
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2085-2088,
June, 1960
Original article submitted June 25, 1959

The alkaloid cinchonamine was isolated in 1881 from the bark of the cinchona tree Remijia Purdieana by M. Arnaud [1]. The empirical formula he found for the alkaloid was confirmed in 1884 by O. Hesse [2]. However, the structure of cinchonamine was established only in 1950 [3]. Cinchonamine differs in structure from most cinchona alkaloids in that it is an indole derivative. A study of the biogenetic connection of alkaloids indicated that there is a close structural relation between cinchona alkaloids of the quinoline series, cinchonamine, and indole alkaloids [4]. This was later demonstrated by the synthetic conversion of dihydroquinone into 5-methoxydihydrocinchonamine and dihydrocinchonine into dihydrocinchonamine [5, 6] and also by the fact that the same conversion products were obtained from dihydrocinchonamine and dihydrocorynantheol [7, 8]. In this connection, the synthesis of the alkaloid cinchonamine is of particular interest.

We synthesized natural, optically active (+)-cinchonamine [9] from the ethyl ester of (+)-3-vinylquinuclidine-8-carboxylic acid [10] and butyrolactone by the scheme described previously for the pyridine analog of cinchonamine [11].



Condensation of the ethyl ester of (+)-3-vinylquinuclidine-8-carboxylic acid (I) with γ-butyrolactone (II) led to α-(3-vinylquinuclidoyl-8)-γ-butyrolactone (III). When the latter was heated with dilute sulfuric acid, decarboxylation occurred and ω-hydroxypropyl 3-vinylquinuclidyl-8 ketone (IV) was formed. The phenylhydrazone was obtained by the action of phenylhydrazine on (IV) in alcohol or ether. Heating the phenylhydrazone (V) with an alcohol solution of sulfuric acid yielded cinchonamine (VI). The physicochemical properties and color reactions of synthetic, optically active cinchonamine coincided completely with those given in the literature for the natural alkaloid.

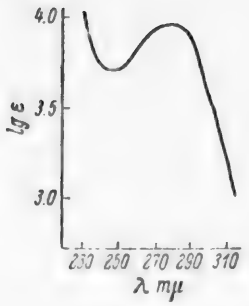


Fig. 1. Ultraviolet absorption spectrum of (+)-cinchonamine in alcohol.

EXPERIMENTAL

α-(3-Vinylquinuclidoyl-8)-γ-butyrolactone (III). A mixture of 5.5 g of the ethyl ester of (+)-3-vinylquinuclidine-8-carboxylic acid with b.p. 80-82° (0.5 mm), d^{20}_4 1.0280, $n^{20}D$ 1.4850, $[\alpha]^{21.5}D$ + 69.58 (c 1.006, 95% C_2H_5OH) and 2.94 g of γ-butyrolactone (b.p. 75-80° at 7 mm and $n^{20}D$ 1.4356) was added with vigorous stirring to a suspension of 2.33 g of dry sodium ethylate in 30 ml of anhydrous benzene. The temperature of the reaction mixture rose spontaneously to 40°. After an hour, the temperature was raised to 80-85° and kept there for 2 hr. On the following day, 15 ml of water was added to the reaction mixture. The benzene layer was separated and washed with water. The aqueous layer was acidified to Congo with dilute hydrochloric acid (1 : 1) and extracted repeatedly with benzene. The aqueous layer was then neutralized with saturated potassium carbonate and extracted with chloroform. From the benzene extract we obtained 1.42 g of unreacted ethyl ester of (+)-3-vinylquinuclidine-8-carboxylic acid. Removal of the solvent from the chloroform extract and distillation of the residue yielded α-(3-vinylquinuclidoyl-8)-γ-butyrolactone as a colorless, viscous, oily liquid, which was readily soluble in ether, alcohol, benzene, and water and crystallized on standing. The yield was 1.73 g (35.7%).

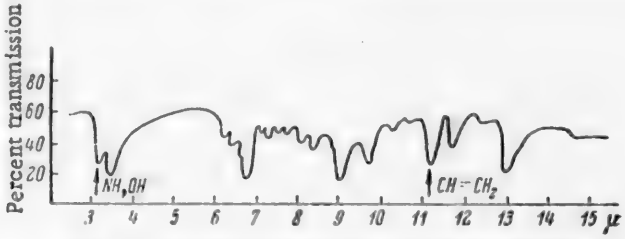


Fig. 2. Infrared spectrum of (+)-cinchonamine.

B.p. 152-153° (0.5 mm), m.p. 60-62° (deformed at 55°), $[\alpha]^{20}D$ + 83.6° (c 1.56, 96% C_2H_5OH);

λ_{max} (C_2H_5OH) 285 mμ, log ε 3.46; λ_{min} (C_2H_5OH) 245 mμ, log ε 2.79.

Found %: C 67.21, 67.32; H 7.96, 7.98; N 5.61, 5.57. $C_{14}H_{19}O_3N$. Calculated %: C 67.45; H 7.68; N 5.62.

The reineckate of α-(3-vinylquinuclidoyl-8)-γ-butyrolactone had m.p. 152.5-154° (decomp.).

Found %: C 38.21, 38.35; H 4.43, 4.74; N 17.14, 17.20. $C_{14}H_{19}O_3N \cdot C_4H_7N_6S_4Cr$. Calculated %: C 38.03; H 4.61; N 17.25.

ω-Hydroxypropyl 3-vinylquinuclidyl-8 ketone (IV). A mixture of 0.96 g of α-(3-vinylquinuclidoyl-8)-γ-butyrolactone and 6 ml of 2 N sulfuric acid was heated at 120° until the evolution of carbon dioxide ceased (about 1 hr). The cooled reaction mixture was treated with ether, then neutralized with potassium carbonate and extracted with ether. The extract was dried with sodium sulfate and the ether removed. The residue was a light yellow liquid. The yield was 0.6 g (70.3%). The crude ω-hydroxypropyl 3-vinylquinuclidyl-8 ketone was used for preparation of the phenylhydrazone.

Phenylhydrazone of ω-hydroxypropyl 3-vinylquinuclidyl-8 ketone (V). a) A mixture of 0.43 g of ω-hydroxypropyl 3-vinylquinuclidyl-8 ketone and 0.208 g of freshly distilled phenylhydrazine in 2 ml of alcohol was heated at 80-85° for 14 hr. The alcohol was removed in vacuum. The residue was ground repeatedly with water and dried in a desiccator. The yield was 0.48 g (71.5%). The phenylhydrazone base crystallized with a molecule of water. It was readily soluble in alcohol, ether, and benzene, but insoluble in water. It had m.p. 43.5-45°.

Found %: C 69.13, 68.90; H 8.61, 8.33; N 12.58, 12.55. $C_{19}H_{27}ON_3 \cdot H_2O$. Calculated %: C 68.85; H 8.82; N 12.68.

The reineckate of the phenylhydrazone had m.p. 136.5-138° (decomp.) (from aqueous alcohol).

Found %: C 43.36, 43.80; H 5.28, 5.33; N 20.00, 19.80. $C_{19}H_{27}ON_3 \cdot C_4H_7N_6S_4Cr$. Calculated %: C 43.65; H 5.42; N 19.92.

b) A mixture of 0.235 g of ω-hydroxypropyl 3-vinylquinuclidyl-8 ketone and 0.193 g of freshly distilled phenylhydrazine in 5 ml of dry ether was heated at 80° for 18 hr. The ether was removed and the residue ground with water and dried in a desiccator. The yield was 0.330 g (almost quantitative).

M.p. 41.42°. $[\alpha]^{20}D$ + 155° (c .967 C_2H_5OH); λ_{max} (C_2H_5OH) 270 mμ; log ε 4.09; λ_{min} 240 mμ; log ε 3.56.

Found %: C 72.48, 72.77; H 8.23, 8.28; N 13.44, 13.48. $C_{19}H_{27}ON_3$. Calculated %: C 72.81; H 8.68; N 13.41.

(+)-Cinchonamine. To 0.3 g of the base of the phenylhydrazone of ω-hydroxypropyl 3-vinylquinuclidyl-8 ketone were added 5 ml of anhydrous alcohol and 0.4 ml of concentrated sulfuric acid. The mixture was heated for 1 hr at 60°. The reaction mixture acquired a dark green color. When cool, it was carefully neutralized to Congo with an alcohol solution of ammonia. The ammonium sulfate precipitate was removed. The residue after removal of the alcohol was treated with an aqueous solution of potassium carbonate. The base liberated was extracted with ether. The extract was dried with potassium carbonate. Removal of the solvent left a light yellow oil, which was ground with a small amount of alcohol to yield a colorless, crystalline base that was readily soluble in hot alcohol, ether, and chloroform; it was less soluble in cold alcohol and insoluble in water and ligroin. The base gave a red color with Ehrlich's reagent.

M.p. 196°, $[\alpha]^{21}D$ + 120° (c 0.208, C_2H_5OH); λ_{max} (C_2H_5OH) 280 mμ, log ε 3.98; λ_{min} 247 mμ, log ε 3.71.

Found %: N 9.16, 9.63. $C_{19}H_{24}ON_2$. Calculated %: N 9.45.

The tartrate of (+)-cinchonamine had m.p. 85° (deformed at 55°).

Found %: C 61.98; H 6.91; N 6.31. $C_{19}H_{24}ON_2 \cdot 2C_4H_6O_6$. Calculated %: C 61.87; H 6.77; N 6.28.

SUMMARY

Natural, optically active (+)-cinchonamine was synthesized.

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SYNTHETIC INVESTIGATIONS OF ISOMERIC COCAINES

VI. SYNTHESIS OF METHYL ESTERS OF TROPAN-3β-OL-2-α-CARBOXYLIC ACID, PSEUDOECGONINE, AND TROPAN-3β-OL-2β-CARBOXYLIC ACID, ECGONINE

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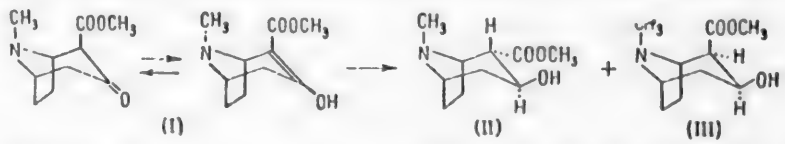
Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2088-2091, June, 1960
Original article submitted June 12, 1959

In a previous communication [1] we described the catalytic hydrogenation of the methyl ester of tropan-3-one-2-carboxylic acid to the axial 3-hydroxy methyl esters of alloecgonine and allopseudoecgonine.

There has been little study of the electrochemical reduction of tropan ketones and there is little in the literature on this subject. Thus, for example, in the patent [2] it is stated that the electrochemical hydrogenation of tropinone on lead electrodes in an acid medium yields equatorial tropan-3β-ol, pseudotropine, while under analogous conditions, but in an alkaline medium, the reaction product is axial tropan-3α-ol, tropine [3]. According to patent data, the electrochemical reduction of the methyl ester of tropan-3-one-2-carboxylic acid on lead electrodes in an acid medium yields equatorial 3-hydroxy isomers: the methyl ester of pseudoecgonine and the methyl ester of ecgonine [4]. Our experiments on the electrochemical reduction of N-methyl-3-carbomethoxy-4-piperidone on a lead cathode in alkaline medium lead to a mixture of axial (18.8%) and equatorial (12%) N-methyl-3-carbomethoxy-4-hydroxypiperidones [5]. Similar results, but with the predominant formation of pseudoecgonine, were obtained by reduction of the methyl ester of tropan-3-one-2-carboxylic acid. There results indicate that the roles of sterically directed electrochemical hydrogenation, depending on the pH of the electrolyte, are common to tropan ketones.

The chemical reduction of the keto group of the tropan compounds has been described in adequate detail in the literature. Among the work in this field, we should mention hydrogenation with zinc and hydriodic acid [6], sodium in alcohol [7], aluminum isopropylate [8,9], complexes of metal hydrides [9, 10], and sodium amalgam [11]. Mainly equatorial 3-hydroxy alcohols or mixtures of them with the axial isomers were formed in all these cases.

In the present work we investigated the chemical hydrogenation of the methyl ester of tropan-3-one-2-carboxylic acid (I) to the methyl esters of tropan-3-ol-2-carboxylic acids and the separation of the mixtures of equatorial 3-hydroxy isomers into individual substances: the methyl ester of tropan-3β-ol-α-carboxylic acid, pseudoecgonine (II), and the methyl ester of tropan-3β-ol-2β-carboxylic acid, ecgonine (III).



Reduction of the methyl ester of tropan-3-one-2-carboxylic acid with electrolytically prepared sodium amalgam yielded an oily liquid, which corresponded in analyses and constants to a mixture of the methyl esters

of equatorial tropan-3β-ol-2-carboxylic acids (II) + (III). Separation of the precipitate which formed as the mixture stood [the methyl ester of pseudoecgonine (II)] and fractional distillation of the remaining oily material yielded the methyl ester of ecgonine (III).

Thus, as in the hydrogenation of N-methyl-3-carbomethoxy-4-piperidone [5], the chemical reduction with sodium amalgam formed mainly 3-equatorial alcohols.

EXPERIMENTAL

Methyl esters of tropan-3-ol-2-carboxylic acids, pseudoecgonine and ecgonine (II) and (III). For the preparation of sodium amalgam we used an electrolyzer [12] containing a mercury cathode, a nickel anode, and 40% sodium hydroxide solution. The current strength was 28-30 a and the potential difference was 7-8 v. The electrolyzer with the sodium amalgam prepared in it served as a reactor for reduction. A solution of 15 g of the methyl ester of tropan-3-one-2-carboxylic acid in 150 ml of 10% sulfuric acid was cooled to −5° and added to 2.6 kg of 1.3-1.5% sodium amalgam. The reduction was carried out with vigorous stirring at from −2 to + 2° and the acidity of the medium was maintained within the pH range 3-3.5 by the addition of 25% sulfuric acid. The acid consumption was about 300 ml. The reduction was continued for about 2 hr until 3 drops of the reaction mixture no longer gave a color with a 10% aqueous solution of ferric chloride. It should be noted that the reaction was accompanied by frothing and the formation of a precipitate. At the end, 130 g of potassium carbonate was added at a temperature not higher than 15°, the reaction mixture separated from the mercury, and the substance extracted with chloroform (5 × 200 ml). The experiment was repeated twice with the same quantities. The extract was dried with sodium sulfate. Removal of the solvent yielded 44.3 g of an oily liquid, from which the methyl ester of pseudoecgonine began to crystallize on standing (1-2 days at 0°) or when a seed was added. For separation of the isomeric esters of ecgonine, the crystal-filled mass was mixed with an equal volume of absolute ether and the precipitated methyl ester of pseudoecgonine separated. The yield was 9.7 g (21.3%).

I. Methyl ester of pseudoecgonine (II). The base had m.p. 128-130° (from ethyl acetate). It had subl. p. 108-110° (0.5 mm).

Found %: C 60.39; H 8.47; N 6.82. $C_{10}H_{17}O_3N$. Calculated %: C 60.28; H 8.59; N 7.02.

The hydrochloride had m.p. 212-214° (from methanol).

Found %: C 51.18; H 7.71; N 5.74. $C_{10}H_{18}O_3NCl$. Calculated %: C 50.95; H 7.69; N 5.94.

A mixture of the hydrochloride of the methyl ester of pseudoecgonine (m.p. 212-214°) with the hydrochloride of the methyl ester of allopseudoecgonine (m.p. 188-189.5°) had m.p. 176-177°.

The picrate had m.p. 132-134.5° (from dry methanol).

Found %: C 44.54; H 4.81; N 13.22. $C_{16}H_{20}O_{10}N_4$. Calculated %: C 44.87; H 4.71; N 13.08.

A mixture of the picrate of the methyl ester of the pseudoecgonine (m.p. 132-134.5°) with the picrate of the methyl ester of alloecgonine (m.p. 126-131°) had m.p. 112-125°, while a mixture with the picrate of the methyl ester of allopseudoecgonine (m.p. 196-198°) had m.p. 129-159°.

II. Methyl ester of ecgonine (III). To obtain the base, we distilled the solvent from the filtrate after separation of the methyl ester of pseudoecgonine. The residue (33 g) was fractionated. The first fraction was the methyl ester of ecgonine. The yield was 15.4 (33.9%).

B.p. 84-88° (0.2 mm), d^{20}_4 1.1497, $n^{20}D$ 1.4890, MR_D 50.01; calc. 51.10.

Found %: C 60.50; H 8.72; N 7.01. $C_{10}H_{17}O_3N$. Calculated %: C 60.28; H 8.59; N 7.02.

The hydrochloride had m.p. 199-200° (from dry methanol).

Found %: C 50.87; H 7.85; N 5.72. $C_{10}H_{18}O_3NCl$. Calculated %: C 50.95; H 7.69; N 5.94.

A mixture of the hydrochloride of the methyl ester of ecgonine (m.p. 199-200°) with the hydrochloride of the methyl ester of allopseudoecgonine (m.p. 188-189.5°) had m.p. 173-174°, while a mixture with the hydrochloride of the methyl ester of pseudoecgonine (212-214°) had m.p. 182-185°.

The picrate had m.p. 140.5-144° (from dry methanol).

Found %: C 44.48; H 4.86; N 12.98. $C_{16}H_{20}O_{10}N_4$. Calculated %: C 44.87; H 4.71; N 13.08.

A mixture of the picrate of the methyl ester of ecgonine (m.p. 140.5-144°) with the picrate of the methyl ester of allopseudoecgonine (196-198°) had m.p. 130.5-161°, while a mixture with the picrate of the methyl ester of alloecgonine (m.p. 126-131°) had m.p. 107-120° and a mixture with the picrate of the methyl ester of pseudoecgonine (m.p. 132-134.5°) had m.p. 103-115°.

The methyl ester of ecgonine was isolated from its hydrochloride and its picrate.

B.p. 84-86° (0.2 mm), d^{20}_4 1.1469, $n^{20}D$ 1.4880, MR_D 50.00; calc. 51.10.

Mixture of methyl esters of ecgonine and pseudoecgonine. The yield was 8.8 g (19.3%) (second fraction).

B.p. 88-94° (0.2 mm), d^{20}_4 1.1563, $n^{20}D$ 1.4922, MR_D 50.09; calc. 51.10.

SUMMARY

1. The chemical hydrogenation of the methyl ester of tropan-3-one-2-carboxylic acid to the methyl esters of isomeric tropan-3-ol-2-carboxylic acids was studied.

2. It was shown that the reduction is stereodirected and yields equatorial 3-hydroxy isomers: the methyl ester of tropan-3β-ol-2β-carboxylic acid, ecgonine.

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LETTER TO THE EDITOR

SYNTHESIS OF β-(2,4-DINITROPHENYL)-ETHYL HALIDES

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Translated from Zhurnal Obshchei Khimii, Vol. 30, No. 6, pp. 2091-2092,
June, 1960
Original article submitted February 2, 1960

In continuing our study of color in compounds with separated chromophoric systems [1], we needed to synthesize as intermediate products β-(2,4-dinitrophenyl)-ethyl halides. Attempts by a number of authors [2] to prepare the corresponding 2,4-dinitrobenzyl bromide by nitration of 4-nitrobenzyl bromide were unsuccessful as oxidation occurred and bromine was liberated. We observed an analogous phenomenon in the synthesis of β-(2,4-dinitrophenyl)-ethyl bromide.

In developing a procedure for the synthesis of β-(2,4-dinitrophenyl)-ethyl chloride, we considered the peculiarities of the preparation of the corresponding bromide and 2,4-dinitrobenzyl chloride [3]. We were able to obtain these preparations in a pure form only after many experiments in which we varied the nature of the nitration mixture, its concentration, and the reaction temperature and time.

We synthesized β-(2,4-dinitrophenyl)-ethyl bromide in the following way: To a solution of 4.6 g (0.02 mole) of β-(4-nitrophenyl)-ethyl bromide in 15 g of H_2SO_4 (monohydrate) was added a nitration mixture of 2 g of fuming nitric acid and 4 g of H_2SO_4 (monohydrate) with stirring. The temperature did not exceed 15° during the addition of the nitration mixture. The reaction mixture was stirred for 3 hr at 15°, poured onto ice, and extracted with benzene. The extract was washed with water until neutral and the benzene removed. After being frozen at −5° for two days, the red-orange oil deposited crystals of β-(2,4-dinitrophenyl)-ethyl bromide. The substance was recrystallized from a mixture of ligroin and ether. The yield was 0.96 g (20%) and the m.p. was 34°.

Found %: N 10.31, 10.45. $C_8H_7O_4N_2Br$. Calculated %: N 10.2.

Due to the greater stability of β-(2,4-dinitrophenyl)-ethyl chloride, we synthesized it under more drastic conditions in a considerably better yield. After the nitration mixture had been added, the reaction mixture was kept at room temperature for a day and then stirred at 40° for 5 hr. The yield was 89% and the m.p. 23.5°.

Found %: 12.4, 12.44. $C_8H_7O_4N_2Cl$. Calculated %: N 12.24.

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